

ANTIMICROBIAL RESISTANCE
PUBLIC MEETING
PRE-APPROVAL STUDIES AND PATHOGEN LOAD
BREAKOUT GROUP DISCUSSION - MONOGASTRICS

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I N D E X

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February 24, 2000

PAGE:

DISCUSSION/QUESTION/ANSWER

3

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BREAKOUT GROUP DISCUSSION - MONOGASTRICS

(2:00 p.m.)

DISCUSSION/QUESTION/ANSWER

CHAIRMAN MORRISON: Can we come back to this because I think this might -- you might want to have this discussion on tape, I'm guessing. And if we can come back to these points in just a moment. Okay. Is that all right?

MR. SCHUSTER: I just wanted to comment --

CHAIRMAN MORRISON: Well, let's hold off because I think it's valuable discussion. So we're going to come --

(Pause.)

CHAIRMAN MORRISON: Yes; we're taping now?

REPORTER: Yes, we're on.

CHAIRMAN MORRISON: Okay.

MR. SCHUSTER: Let me interrupt and give you some background because we came up with these yesterday.

MR. ANDRES: Sure.

MR. SCHUSTER: Dale Schuster, Schering-Plough. I just want to comment on Paula. When we came up with these yesterday, a lot of us, our feelings were that there really weren't many pre-approval studies, perhaps none that you can envision, that really were relevant.

And so, what we came up with was things that would be nice -- baseline information, background information, might support post-approval studies, would not be too difficult to

1 conduct and that interpretation would be rather straightforward
2 because they were rather standard things to do.

3 For instance, the mutation rates of resistance in
4 vitro, it's very common to do that. It's standard procedures,
5 maybe not an accepted, validated method, but it wouldn't be
6 that hard to get from there. So these were some of the things
7 that could be done that might be of some use.

8 I think that -- I personally fully agree with you
9 that many of these things, and perhaps all of them, have
10 questionable relevance but our view was that these could be
11 done and it's not uncommon to do them and maybe not that out of
12 line to expect sponsors to try to generate that sort of data as
13 a background package going into a new chemical entity type of
14 thing.

15 DR. FEDORKA-CRAY: I think --

16 CHAIRMAN MORRISON: Okay, Paula; could you use the
17 microphone because --

18 DR. FEDORKA-CRAY: Well, I mean, I think that -- my
19 point was is that I think that as you're putting something
20 forward that you would want to -- that you would want to just
21 make clear that this could or this -- this would or this would
22 not be part of an approval package and it's not --

23 I mean, is it going to answer the question if there's
24 a risk to human health if you're not going to define, you know,
25 in your objectives what bugs you're looking at, because you

1 could end up with a whole list of, you know, aerobic and
2 anaerobic commensals and other types of pathogens and whatnot.

3 And so, you know, to me, one of the questions that
4 should be posed would be exactly what are we doing here as far
5 as looking at -- you know, what bacteria are you even willing
6 to propose relative to the drug because the drug is being
7 proposed for a target pathogen and that the drug may not have
8 any relevance for some of these other mechanistic type
9 features.

10 And so, you know, I think that you just want to --
11 you know, you want to lay it out so that it's -- they're
12 achievable and that the expectation is, is that you're not
13 going to be reinventing the wheel, you know.

14 Many of these tests -- in fact, like I said, I think
15 you already know the mechanism of resistance when you're
16 looking at the class of drugs, but you may not have much of an
17 idea of some of the effects that are going to happen with other
18 bugs or how that would even interact with some other
19 antimicrobials over time.

20 CHAIRMAN MORRISON: Paula, that's actually going to
21 be a question that we're going to be getting to in probably
22 about an hour -- what pathogens and should we consider other
23 organisms?

24 DR. FEDORKA-CRAY: So, I don't -- I just don't see
25 these as an objective toward answering the questions, toward

1 answering the -- you know, these are study considerations but
2 not necessarily an objective of the package.

3 CHAIRMAN MORRISON: Okay. So if I understand, your
4 point would be that perhaps points one, two and three are
5 studies or types of studies that would support the objective of
6 characterizing the rate and development of resistance. Not
7 really objectives by themselves, but studies that would support
8 that objective. Perhaps point five is more of an objective.

9 DR. FEDORKA-CRAY: I would say point five would be
10 the objective.

11 CHAIRMAN MORRISON: Scott.

12 DR. McEWEN: Scott McEwen. But we heard from
13 CVM yesterday that they were going to do that before the
14 pre-approval studies, weren't they?

15 DR. FEDORKA-CRAY: Right.

16 DR. McEWEN: And we made the point that some of this
17 information might be used to, in a sense, validate that initial
18 categorization or invite the opportunity for reconsideration or
19 something?

20 DR. FEDORKA-CRAY: I would change -- I agree with
21 Scott; I would change the wording on categorizing. You're
22 going to know the categorization before, I think, you even
23 submit the drug for approval.

24 CHAIRMAN MORRISON: Well, as long as we're -- this
25 was presented as a slate of five. Now, as long as we're sort

1 of modifying that, we actually could delete the fifth one
2 because we've got our input earlier where we said we hoped this
3 information will influence or be able to influence the
4 categorization. Is that --

5 DR. FEDORKA-CRAY: Don't you think that you're going
6 to have -- really, pre-approval studies --

7 CHAIRMAN MORRISON: Oh, I'm sorry. You should use
8 the microphone again.

9 MR. ANDRES: Just bring the chair up here, Paula.

10 (Laughter.)

11 MR. ANDRES: You have to use the microphone,
12 otherwise you don't get recorded --

13 DR. FEDORKA-CRAY: Paula Cray. I think that -- I
14 mean, I think the categorization issue is even up -- that it's
15 not fully determined yet, and so, how would that be an
16 objective of a pre-approval study if that already has to be
17 sort of a priori information?

18 CHAIRMAN MORRISON: The thought was that --

19 DR. FEDORKA-CRAY: And that, yes, I think that if
20 you're going to design a pre-approval study, you're going to
21 look at probably just doing it for a category one type drug
22 because category two type drugs probably aren't going to
23 require anything. Category threes aren't going to require
24 anything, and if there in fact are categories such as one, two
25 and three.

1 So I'm not -- I mean, I don't know -- designed to
2 modulate how a compound is ultimately categorized, you have to
3 know that information prior to going into the pre-approval
4 study. So if you're setting up the study, you just want to set
5 up and say, okay, this is how we're going to do it.

6 CHAIRMAN MORRISON: The thought was that let's say
7 you have a compound that comes in and it's going to be used in
8 category three and then they find out, holy smokes, while it's
9 a great compound, it's really got some implications for humans
10 that we didn't expect; perhaps we should put it into two or one
11 at the end of the pre-approval studies or opposite, comes in in
12 one and you find out it's got zero risk for people, even -- and
13 you know, so you might reevaluate the final use or category.

14 DR. FEDORKA-CRAY: Well then, that brings up a
15 question that I would say is, do you need pre-approval studies
16 at all? And that was discussed in some of the other sections
17 yesterday. I mean, do we really need a pre-approval study at
18 all because ultimately, drugs may be moved, re-categorized at
19 any period in time.

20 And so, if you're going outside of the box, then are
21 you going to focus most of your efforts on a post-approval type
22 monitoring system where you -- you know, you're looking at the
23 rate of resistance developing along those lines.

24 I mean, that would be a question I would ask -- what
25 kind of support is there for looking at these types of studies

1 at all, you know, designed as they are. And that's not to say
2 that the companies don't come forward and say, this is what
3 we've done, you know, much along the same lines that they've
4 been doing now. But, jumping through other types of studies,
5 is it going to ultimately get you where you want to go?

6
7 CHAIRMAN MORRISON: So perhaps, Chuck, we could add a
8 point in the general area that if post-approval studies are
9 going to be intensive and vigilant, etcetera, there's a
10 question of the value of pre-approval studies. Is that your
11 point?

12 DR. FEDORKA-CRAY: Yes.

13 CHAIRMAN MORRISON: Okay. And I want to clarify this
14 one -- if, in the general considerations, if post-approval
15 studies are going to be in-depth and robust, etcetera, there's
16 a question of the value of pre-approval studies. Okay.

17 If there's going to be pre-approval studies, would
18 you support or do you think the idea of using the information
19 that you generate in pre-approval studies to influence the
20 final categorization of drugs is a valid point. Is that -- not
21 that you say or nay. Some people did. That's the
22 understanding on that point. That's the point of it.

23 DR. FEDORKA-CRAY: Again, I would say that that's
24 more of a consideration or a general point rather than
25 objective. You won't know that until the end of what you're

1 doing anyhow. I mean, your objectives are how do you assess
2 the rate and extent -- I mean, the impact on human health, and
3 that sort of falls out last.

4 CHAIRMAN MORRISON: Okay. Is there feeling from
5 whoever that was --

6 DR. BROWN: Right here.

7 CHAIRMAN MORRISON: Was it Scott or Robin?

8 MR. ANDRES: I think it was Scott.

9 CHAIRMAN MORRISON: Scott. Do you have a feeling on
10 that, Scott?

11 DR. BROWN: Scott Brown, Pharmacia & Upjohn. Just
12 for context, I think what we were talking about yesterday was
13 that the class and the proposed usage of a compound would
14 generally cause it to be put into a particular category at the
15 very beginning of the drug development process.

16 DR. FEDORKA-CRAY: That's right. So you don't need a
17 categorization.

18 DR. BROWN: It's already done provisionally. Let's
19 put it that way. Then the data we're talking about would be
20 used to -- in this case, what I've used -- I've used the word
21 modulate that categorization, either upwards or downwards,
22 depending upon whether the compound is acting in expected
23 manner for other compounds in that class or whether that usage
24 is now being shown through whatever data to be posing an
25 extraordinarily higher exposure to human zoonotic organisms and

1 so forth or less, and that ultimately there's going to be a
2 transition from a provisional categorization to a "final"
3 categorization.

4 I use that word in quotes because you're right,
5 Paula, it's going to change over time depending upon the human
6 drug usage and depending upon the data that's captured post-
7 approval.

8 But in essence, a final categorization that then
9 drives perhaps the threshold for the post-approval monitoring.
10 Perhaps it drives the degree of vigilance in the post-approval
11 monitoring, and perhaps drives the ways the compound might be
12 used in the field.

13 That was the idea of this battery of tests and that
14 throughout the process, the sponsor would be able to discuss
15 and reach concurrence with the Agency about what decisions will
16 be made from these kind of studies, that we'd have a clear
17 decision criteria before we would embark on these studies to
18 know exactly what it is that the Agency is going to decide
19 based upon the outcomes. So that was -- that's the context
20 that we had for yesterday.

21 Again, when we got the notion from the Agency that
22 these studies are pivotal, then the question was, well, if
23 they're pivotal, that means that the Agency is using them to
24 make decisions, arguably, during the FOI, and then you say, how
25 do you write the FOI?

1 But, if they're being used for decision making, then
2 the sponsor wants to know how those decisions are being made, a
3 priori, and that's I think, the point where we'd like to make
4 sure that that's done, not of the end game, because then all
5 the money is sunk, but rather up front where you know how you
6 can adjust the battleship prior to its reaching its port.

7 MR. ANDRES: Chuck Andres, CVM. And Scott, I think
8 we put that under the general comments point number three,
9 standards for acceptance of pre-approval studies would be set a
10 priori?

11 DR. BROWN: Yes.

12 DR. BROWN: One more comment, and that is that
13 the comments that were made in a couple of the other groups
14 that, well, pre-approval studies really aren't necessary, and I
15 think that was what came out of the other -- two of the other
16 groups.

17 I guess we sort of didn't even consider, when we
18 found out that these studies were going to be pivotal, and so
19 we didn't -- I don't know that we even considered whether they
20 could be cast off as being unnecessary.

21 We made the assumption -- at least I made the
22 assumption, personally, that since the Agency said yes, they're
23 pivotal, that they were going to be required in some fashion or
24 other and we're going to try to figure out what to do to take
25 care of that box checking.

1 (Pause.)

2 CHAIRMAN MORRISON: I've just suggested to Chuck, on
3 those three "objectives" that we just sub those in under that
4 major objective that we have of characterizing the rate and
5 extent of development, of resistance development. Studies that
6 might support this or studies that might -- could include one,
7 two, three.

8 (Long pause.)

9 CHAIRMAN MORRISON: So we have three objectives now
10 that we've --

11 MR. SCHUSTER: Dale Schuster, Schering-Plough. I
12 mean, we're proposing these as studies that could be included
13 but I think there's very much an awareness that these aren't
14 really going to do a very good job of characterizing the rate
15 and extent of resistance development that you'd predict in the
16 field.

17 I'm not sure if we want to leave it exactly like this
18 or mention that that's a clear caveat of what studies we're
19 proposing there.

20 DR. BYWATER: Robin Bywater, Pfizer. I think the
21 problem with all this is that we're going to be presented if,
22 if we're not careful, with the Agency setting criteria for
23 acceptance or rejection of one of these studies.

24 Calling it pivotal and hanging the compound on the
25 basis of the fact that you can transfer resistance and that

1 resistance does develop -- I mean, the expectation is that
2 these will be positive findings in a sense.

3 It's a question of how you interpret them; and
4 therefore, I think the concern is very much that the pivotal
5 nature of these studies implies setting criteria. In fact,
6 Scott said we need criteria; in one sense we do.

7 But the awful danger is that those criteria will be
8 so easily incorporated into a negative decision that it'll come
9 back to haunt us, and maybe the complications of doing these
10 programs in full, which is what Paula was referring to -- I
11 mean, you can do these in a relatively simplistic way and the
12 way that I think we would normally expect to do, at least
13 something of these.

14 But if you want to do it fully and exhaustively,
15 you're into a huge amount of work, even in an in vitro context,
16 and lots and lots more questions.

17 CHAIRMAN MORRISON: So, are you questioning, Robin,
18 the value of putting these at all or cushioning the language
19 or --

20 DR. BYWATER: I just think we should make it clear
21 that this is informational and we shouldn't be setting
22 unreasonable criteria for passing and failing at these stages.
23 It ought to be part of the overall evaluation which is the way
24 we referred to it before we were given this dreadful word
25 pivotal to hang onto them.

1 And as part of the overall evaluation, it would help
2 in the categorization. It would help in the design of the
3 post-approval monitoring, which I think we all agree is the
4 key.

5 CHAIRMAN MORRISON: Mike.

6 MR. ANDRES: If I could maybe allay a little bit of
7 fears and uncomfortableness, if we think of -- I've been trying
8 to think of a good analogy and I'll probably get kicked for
9 this one but drug residues -- okay. The fact that a drug
10 produces "residue" doesn't render it unapprovable. Okay.

11 And risk assessments are made based on the residue
12 present, amount, the toxicology of the amount and its effect it
13 could have on humans. And I think as we go down this road on
14 the resistance issues, the same type of thought process will
15 probably be used.

16 The fact that you show resistance may not be a
17 trigger to say it's unapprovable. It may lead us to, okay,
18 what next question needs to be answered before it satisfies our
19 need to protect the public health?

20 So, I don't think it's, you know, okay, this box is
21 checked, or it's a defined decision tree. If the answer is
22 yes, go home, take your drug and go home. I don't think it's
23 -- I know it's not that. So as we finalize writing any
24 guidance associated with this, certainly that will be taken
25 into consideration.

1 DR. REDMAN: Sharon Redman, Novartis Animal Health.
2 Just to Robin's point, then, maybe -- on that first objective
3 with the studies, that one of his points should be that -- as
4 far as, you know, studies could include or you could have
5 evaluations of studies would be a part of the overall risk
6 assessment, not pass/fail. Just to make sure that those
7 concerns are addressed when you deliver this message.

8 CHAIRMAN MORRISON: Okay.

9 DR. REDMAN: In other words, you have studies --
10 could include -- you could have another thing that says
11 evaluation of studies would be -- or, you know, some -- you
12 know, it would be considered in the risk assessment, and thus
13 would not be pass/fail, because that is a major concern.

14 You know, how can we set a pass/fail when we don't
15 know, really, what pass/fail is? We don't know the relevance.
16 We don't know how these will play out in predictability, so
17 how can we have pass/fail at this point? So, we need to
18 continue to expand our database. We need to get to that point
19 where you could even do a mathematical model. We're not there
20 yet.

21 CHAIRMAN MORRISON: Okay.

22 DR. REDMAN: Really, that wasn't why I walked up
23 here, though.

24 (Laughter.)

25 DR. REDMAN: So basically, on the point about the

1 classifications, on the next slide -- yeah. Just maybe to,
2 once again in our communications, Scott, as far as design to
3 modulate how a compound is ultimately categorized, maybe we
4 should use the word optimize because that way we link that into
5 -- what we're trying to talk about is dose use rate, those
6 types of things.

7 In other words, we're not trying to squeeze it into
8 one category or another. What we're trying to do is
9 scientifically say, okay, if I do this, if I change the usage,
10 if I change the dosage, whatever, I will make a real difference
11 on the human health hazard, just like we were talking about
12 optimization, the dose and that type of thing. So that was
13 just my suggestion, to change modulate to optimize. That's it.

14 CHAIRMAN MORRISON: Either to change modulate to
15 optimize or design, modulate how a compound is ultimately and
16 optimally categorized? Whichever?

17 DR. REDMAN: The less work the better.

18 DR. McEWEN: Scott McEwen. Just as a follow up to
19 the analogy of the residues, I mean, it could get to the point
20 where it's almost lethal for a drug, I guess. If we had, say,
21 in the analogy of the residues, it's a carcinogen. My sense
22 is, if it is, that almost rules it out as a food animal drug.
23 Right? And in this situation, there might be something that is
24 of that sort of degree of severity.

25 MR. ANDRES: Can you speak up so we can --

1 CHAIRMAN MORRISON: So that, just to kind of round
2 out the analogy, I guess, that yes, we do sort of weigh in the
3 toxicity of the residues and that gets factored into the MRLs
4 and that sort of thing, but there is a threshold which one
5 reaches in that analogy where it kind of makes it untenable for
6 use in food animals and it's possible that that sort of thing
7 would exist in the resistance area as well, but I agree that
8 the industry would want to know that, up front, so that they
9 can sort of weigh that in.

10 CHAIRMAN MORRISON: Just a second, Paula. So did we
11 -- we didn't change that word. Oh, you got -- is ultimate
12 -- oh no, you didn't. Okay. So is there -- Paula.

13 DR. FEDORKA-CRAY: That would be my motion, to change
14 modulate to optimize.

15 CHAIRMAN MORRISON: Well again, we're not seeking
16 consensus but if there's general feeling that that's good, that
17 would be great. Okay. Chuck is saying that optimize is a
18 strong objective and as long as you're aware of that. Okay.

19 MR. SCHUSTER: Dale Schuster, Schering-Plough. I'm
20 not sure I'm comfortable with that change. I'd prefer -- what
21 I heard being said was that it would optimize the dose or the
22 dosing regime or how the drug is used.

23 That's a very different objective than affecting the
24 category. I like modulate the categorization and I think that
25 should stand. But I also like the optimize the dosing regime

1 and I would add that as an additional objective.

2 MR. ANDRES: Okay. So you're suggesting --

3 MR. SCHUSTER: You made the point. Is that -- are
4 you comfortable with that? That's what I understood you to
5 say.

6 DR. REDMAN: Yeah; that was definitely the context of
7 what I was saying. It also goes back to Chuck's point, though,
8 that that is a big objective for us to have, so we've already
9 said that we're not sure how we can optimize efficacy in the
10 antimicrobial resistant safety factors and everything all in
11 the same one.

12 MR. FONDRIEST: Steven Fondriest, Union of Concerned
13 Scientists. Just for clarification, that was one of Fred's
14 points. I'm not sure -- did we take that out?

15 MR. ANDRES: Which?

16 CHAIRMAN MORRISON: I think we've still got it
17 bolded, questioning --

18 MR. FONDRIEST: The optimizing --

19 CHAIRMAN MORRISON: -- whether we could do it.

20 MR. FONDRIEST: Is that the same --

21 MR. ANDRES: This was a study, not an objective.

22 MR. FONDRIEST: Oh, okay.

23 MR. ANDRES: Chuck Andres, CVM. I guess when I heard
24 the optimize, I thought of this bullet and I'm thinking, wait a
25 minute, yesterday we just heard that if we're going to be asked

1 to -- and I just want clarification. I'll type whatever the
2 group would want. I'm just a scribe.

3 But to me there's a disconnect between what we just
4 typed and what's up here in point four, which we discussed for
5 a little bit yesterday. And if it were up to me, optimizing --
6 maximizing the effectiveness of the drug while trying to
7 minimize the resistance, we just said, yesterday, may not be
8 technologically possible. And you know, so whatever you would
9 like, we can modulate that answer.

10 (Laughter.)

11 MR. ANDRES: Scott.

12 DR. BROWN: I really don't want us to get bogged down
13 in some of these semantics because I think the idea is to get
14 the concepts out. Optimizing dose or regimes, to me has always
15 been a bit of a tenuous situation because I don't think there's
16 one size that fits all. We mentioned that earlier for a
17 variety of things.

18 What I think you could do is to optimize the dosage
19 regime with respect to one or the other, either optimize it
20 with respect to efficacy or perhaps optimize it with respect to
21 resistance development in the target organisms.

22 I still don't think we have the wherewithal to
23 optimize the dosage regime with respect to the resistance
24 development in zoonotics. That's the part where I think we're
25 most languishing and where I don't know where the technology

1 will lead us.

2 So, there are some subtle differences in the way
3 those two things are worded, and I understand the desire --
4 we're actually trying to use what we've learned through these
5 studies to better direct the usage of the product. Maybe
6 that's a better way to do it.

7 So maybe instead of optimizing dosage regime, just
8 say, better direct the usage of the product. Is that -- would
9 that work, Sharon? Would that work, Dale? Better direct usage
10 of the product.

11 CHAIRMAN MORRISON: Characterizing the rate of
12 development and resistance and some suggested studies that
13 might address that. Then we've got the objective of the
14 post-approval process, the objective of modulating how a
15 compound is ultimately categorized and the objective of
16 developing information that will best direct the usage of the
17 product. Anything else? What's next, Chuck?

18 MR. ANDRES: This I think we have already, elsewhere.

19 CHAIRMAN MORRISON: Yes. Let's delete the last one.
20 Why don't we just stick that back in the general area? That's
21 where things go. Okay. Those are our objectives and our
22 discussions of our objectives.

23 Then we went onto what data, what role could the
24 various types of data play, and this is where we talked a
25 little bit about mathematical modeling, in vitro studies, in

1 vivo experiments. We didn't really get into field studies, and
2 we talked about the advantages and limitations of those various
3 kinds of data. Okay.

4 MR. ANDRES: Do some quick housecleaning.

5 CHAIRMAN MORRISON: While Chuck's doing that, maybe
6 you just want to refer to your overheads because we're on
7 the --

8 MR. ANDRES: Ready.

9 CHAIRMAN MORRISON: Okay. One (a) is the next one,
10 Chuck.

11 MR. ANDRES: Okay.

12 CHAIRMAN MORRISON: We said, all right, while we
13 recognize that the existing method, 558.15, is not adequate --
14 we said that was --

15 DR. McEWEN: Scott McEwen, University of Guelph. I
16 think the first two are more comments than what are the
17 positive aspects of these concepts, or possibly the first one
18 could be, what are the limitations of the concepts. Like that
19 first one might be stated as a limitation of the 558.15.

20 CHAIRMAN MORRISON: Okay. Why don't we move that --

21 DR. McEWEN: The second one, I think, is more of a
22 comment.

23 CHAIRMAN MORRISON: Yes, that's definitely -- and
24 we've got some view that pathogen load studies should be
25 considered, based -- and remember, we're saying, out of all

1 that stuff that was presented yesterday and the day before,
2 what were the positive things we learned and then what were the
3 limitations that we learned, and there was a view that pathogen
4 load studies should be considered, and about three points
5 later, there was a view that pathogen load studies should be
6 eliminated.

7 So we're passing these comments on again. We learned
8 that mathematical models enable us to test hypothetical
9 scenarios; interventions could fit into a risk assessment. In
10 vitro studies can screen a larger number or a large number of
11 issues and greater controls.

12 Mathematical models, expertise available is limited.
13 I think now we're into limitations. A real concern of the
14 predictability of these pre-approval studies and how they might
15 predict or not predict, what actually might occur in the field.

16 DR. McEWEN: Scott McEwen, University of Guelph.
17 Should we qualify the limited predictability? Does that apply
18 to all pre-approval studies or just one study type because I
19 think we're talking here about the various concepts.

20 And while I'm here, I'd ask, with respect to the
21 mathematical modeling, to me, when I was up here talking
22 yesterday and giving those examples, I was thinking of
23 population models, either deterministic of the --- type.

24 We also have mathematical modeling for pharmacokinetics
25 and dynamics, I guess, that it might -- and whether or not

1 those qualifiers relate to other types of modeling, that it
2 could be at different levels of organization, not population
3 level. Maybe somebody else wants to speak to you, but I was
4 speaking here of the population type modeling.

5 MR. ANDRES: Chuck Andres, CVM. Just so people from
6 a editorial standpoint, when Bob and I sit down to put all this
7 together so that he can present it this afternoon, if specific
8 examples were given about study types, I'll go ahead and put
9 them in bold and that is, as I said before, is the advantage or
10 a limitation, positive or a limitation for that particular
11 individual study type.

12 If there's nothing bolded, it was essentially a
13 generalized comment about all of the studies. So when we talk
14 about what's a limitation, point number three under one (b),
15 limited predictability of what actually occurs in the field, I
16 think the comment yesterday was, that could be related to all
17 of these studies because we -- you know, still, you're
18 predicting. Until it's thrown out in the field, you're really
19 not going to know.

20 DR. McEWEN: Scott McEwen. As long as everybody
21 remembers that, because the way it's laid out here, that kind
22 of could be interpreted to mean -- limited predictability could
23 apply to mathematical models because that's kind of bolded up
24 top when it fact it -- you know, as it's written there, and
25 what you just said, it applies to all of the study types.

1 MR. ANDRES: Well, what we can do is, instead of
2 getting bogged down in kind of ordering, when we sit down to
3 put all this together, we can group all of those that are
4 specifically study oriented comments and those that are general
5 comments about across all studies. Is that satisfactory?

6 CHAIRMAN MORRISON: And when we do that, Scott, your
7 point is mathematical models for simulating populations.
8 That's what you were commenting about.

9 DR. McEWEN: I was. But I was just a little worried
10 that we point out the deficiencies of modeling, which we always
11 do, but we tend not to point out the comparable deficiencies in
12 the other study types.

13 Like, when I said that it requires assumptions, well,
14 we make the same or even larger assumptions about experiments
15 and in vitro studies, but we usually don't state them
16 explicitly so they don't get the same attention.

17 And so, historically, there's been a lot of
18 condemnation of modeling for that reason, when you could make
19 the same, in effect, condemnation of other study types. So
20 it's just the question of balance that we lay out the
21 advantages and disadvantages of all the study types and not
22 sort of pick on one.

23 CHAIRMAN MORRISON: Well, I most certainly heard
24 point three as referring to all these pre-approval -- in vitro,
25 mathematical models, a real concern about the predictability.

1 Point four, that these studies be as robust as necessary to
2 address the objectives.

3 (Pause.)

4 MR. SCHUSTER: Dale Schuster, Schering-Plough. I'm
5 not sure if we're capturing it here or elsewhere, but one
6 comment that I think merits mentioning is that there's a need
7 for validation of any pre-approval studies.

8 If there were validated studies, robust studies, that
9 existed, it might make sense to apply them. It's a deficiency
10 in technology, not a deficiency in need for the studies, I see,
11 and we can make that here or elsewhere.

12 I had maybe just a clarification on what I feel about
13 the pathogen load studies. I guess my view is it's a bit going
14 too far to say that they should be eliminated for the current
15 requirements. I'm much more comfortable in saying that for
16 therapeutic drugs like we're talking about primarily here.

17 It doesn't make sense to add a requirement. So my
18 view, it's not expanding pathogen load studies onto therapeutic
19 drugs. I'm not ready to say whether it does or doesn't make
20 sense to eliminate them for feed additive studies.

21 MR. ANDRES: I guess when that point came up
22 yesterday, there was a feeling that -- on the positive side
23 that they should be considered, which is what I'm hearing you
24 say now, for certain types of compounds, certain types of uses.
25 And a limitation we put down, some people voiced the opinion

1 they should be tossed; they shouldn't be considered at all.
2 And all I'm trying to do is capture -- again, we're not trying
3 to achieve consensus or agreement, other than people who have
4 said what they said. They feel like their voice is being
5 captured here and we're not, you know, skewing the
6 presentation. So, those that felt that --

7 MR. SCHUSTER: I guess --

8 MR. ANDRES: Those that felt --

9 MR. SCHUSTER: I can add --

10 MR. ANDRES: -- pathogen load studies should be
11 eliminated, and I can't remember who brought that point up
12 yesterday. If that's something that, you know, what you've
13 heard today changes your mind, hey, I'm the scribe.

14 MR. SCHUSTER: I would just like to clarify in my
15 mind when we were talking about it, and I don't know if it's
16 true of anybody else, the issue is, should it be eliminated
17 from the Framework document which requires it for all
18 antimicrobials.

19 And I definitely agree with that. I'm not sure that
20 I would want to go so far as to say it should be removed from
21 558.15 studies which are applied solely to growth promotion
22 products. Anybody else, I would be interested in --

23 CHAIRMAN MORRISON: You would suggest we add pathogen
24 load studies should be eliminated for therapeutic applications?

25 MR. SCHUSTER: Should be not -- not applied to

1 therapeutic antimicrobials -- or therapeutic applications uses
2 of antimicrobials.

3 CHAIRMAN MORRISON: Okay.

4 DR. SILLEY: Peter Silley, Don Whitley Scientific. I
5 just think on the pathogen load issue, just carry it on from
6 that. One of the reasons why I believe we're saying that they
7 perhaps ought to just be eliminated completely is because how
8 one interprets the data, the problems, the variability, what
9 the studies actually mean, those are issues and surely they
10 apply to whether we're looking at a therapeutic or something in
11 feed.

12 It's not a rationale in terms of the study type.
13 It's actually just the nature of the data we're generating
14 means it's almost irrelevant, and therefore I would advocate
15 that they should be removed completely.

16 CHAIRMAN MORRISON: So, we better not add that to
17 that -- put it as a separate point? And it gets back to the
18 suggestion earlier, maybe there ought to be a whole discussion
19 or a whole breakout or a whole meeting on this whole pathogen
20 load issue.

21 DR. BYWATER: Robin Bywater, Pfizer. Maybe we could
22 just say pathogen load studies are particularly pointless for
23 therapeutic products. You know, to at least make it quite
24 clear that as far as therapeutic products are concerned, they
25 really don't make any great sense -- short term, high dosage,

1 you know.

2 Anything which is going to be long term, there's at
3 least a possibility, but as Peter says, there really isn't a
4 decent way of testing. The existing method is inhumane,
5 inaccurate and probably misleading.

6 DR. McEWEN: Scott McEwen. They're not limitations
7 as written. Those are comments. They're suggestions. I mean,
8 if you're going to say that the existing pathogen load studies
9 are not predictive or are imprecise or are invalid, then those
10 are limitations. But as written, those are -- it's not stated
11 as limitations.

12 MR. ANDRES: Right. And I think, you know, we go
13 back to the study concepts that were discussed on, I guess now,
14 what -- we're talking Tuesday. It's now Thursday. On Tuesday,
15 what were the positive aspects of those concepts and what were
16 the limitations of those aspects that we heard on Tuesday? And
17 that's what we're trying to capture in answering question -- I
18 guess I've got them numbered as 1(a) and 1(b.)

19 DR. McEWEN: Well, as I said yesterday, I don't think
20 that we were presented information that would allow us to make
21 a judgment about whether they were effective or not. We were
22 just presented with information that said that there were some
23 drugs denied approval, on the basis of those, and some that
24 weren't. But, you know, from an objective sense, there were no
25 data, that I saw, presented that would allow us to make those

1 judgments.

2 DR. FEDORKA-CRAY: Paula Cray. I would agree with
3 Scott that there were not study concepts. There were ideas.
4 There were about 300 questions that were presented. But there
5 was nothing that was presented that could be evaluated. And I
6 would also agree on the pathogen load, should be a separate
7 issue apart from resistance because it's not -- it's a
8 component of resistance but it's not resistance, per se.

9 You know, you're not looking at an MIC. You're not
10 looking at whether it's sensitive or intermediate. It's an
11 effect of antimicrobial use and that's a whole -- that's an
12 entirely separate issue.

13 CHAIRMAN MORRISON: So perhaps what we're hearing is
14 that back in our general, overall comments section we should
15 have pathogen studies -- pathogen load studies should be, sub
16 (1) eliminated because some people feel they should be
17 eliminated. Sub (2) eliminated for therapeutics. Sub (3)
18 included for all, because we've had all views so far.

19 DR. FEDORKA-CRAY: That was just making my comment
20 that I think it should be considered entirely as a separate
21 area, separate from the resistance issue because it's not
22 determining whether the pathogens that you would be affecting
23 in a lone study are resistant or sensitive or -- it has to do
24 with levels and that's entirely different than resistance.

25 CHAIRMAN MORRISON: Okay.

1 DR. FEDORKA-CRAY: It's two separate issues.

2 CHAIRMAN MORRISON: Okay.

3 DR. BYWATER: Robin Bywater. I think Paula's got a
4 good point there. Essentially, pathogen load studies are
5 another aspect of the toxicology, safety program for the drug
6 and it certainly isn't a resistance issue, exactly as she says.
7 And then that is a further reason for eliminating them
8 altogether, from this consideration.

9 CHAIRMAN MORRISON: Okay.

10 DR. McEWEN: Scott McEwen. I think we need to write
11 that comment down as a suggestion or comment, the notion that
12 they be considered separately or in another form or something,
13 because I think everybody seems to agree with that.

14 CHAIRMAN MORRISON: You know, we're doing such a fine
15 job here, you're going to have trouble not just adopting this
16 verbatim. Okay.

17 (Pause.)

18 CHAIRMAN MORRISON: All right. So continuing on our
19 limitations; we're almost done this. I believe, Scott, that's
20 host/environment. A limitation is that in these pre-approval
21 studies, that you have limited ability to evaluate the
22 host/environment factors.

23 MR. ANDRES: This was on an in vivo study, wasn't it?

24 DR. McEWEN: Yeah, I think I was just yakking about
25 different types of studies and said that -- I think it was the

1 in vitro ones, so that -- I think that comment, as I recall,
2 referred to the in vitro.

3 CHAIRMAN MORRISON: In vitro studies?

4 DR. McEWEN: In in vitro studies we have -- we're not
5 as able to look at host/environmental factors. I think that
6 was --

7 CHAIRMAN MORRISON: Does that the duplicate what
8 you've got below, limited because of --

9 DR. McEWEN: I guess so. I mean, I --

10 CHAIRMAN MORRISON: Okay.

11 DR. McEWEN: I didn't have it written down.

12 CHAIRMAN MORRISON: Okay.

13 CO-CHAIRPERSON SINDELAR: I thought I heard you say
14 it was the host, the factors with the host as opposed -- within
15 the factors within the environment and controlled environment
16 as opposed to the variables within a host.

17 DR. McEWEN: Yeah. I mean, yesterday was so long
18 ago. I think we're talking about -- said that we need to
19 consider agent/host/environment issues within -- or it would be
20 ideal to look at those within the context of pre-approval, and
21 that the in vitro studies, sort of by nature, tend to be more
22 useful, I guess, for the agent related issues, although we
23 heard about in vitro modeling of gut ecology and that sort of
24 thing which brings in the -- in some of the environmental
25 issues.

1 That the animal studies, by nature, allow us to look
2 at those host factors and, in general terms, the field studies
3 allow us to look at a bit of more of the environmental -- the
4 contextual stuff, although we can also consider agent and host
5 issues in the field studies. I'm not sure how helpful it is to
6 go down that road very far.

7 But I guess, in general terms, the in vitro studies,
8 they suffer from the generalizability (sic), I guess, or
9 relevance to the real world, as a general statement, and the
10 closer you get to the field studies, the more relevant it is to
11 the real world but the harder it is to interpret and the harder
12 it is to undertake them and the more expensive it is. There's
13 a kind of a hierarchy in that sense, analogous to -- I guess to
14 the sort of development phase where you kind of work up through
15 different species and into clinical trials.

16 CHAIRMAN MORRISON: Okay. So your suggestion is,
17 there's three considerations, the agent, the host and the
18 environment, that in vitro studies are particularly good and
19 appropriate for studying the agent but have their limitations
20 because you can't -- it's difficult to predict, difficult to
21 extrapolate. You've got in vivo studies, expensive, big pig
22 numbers. And environmental studies lack -- difficult for lack
23 of control, all the confounding variables.

24 DR. McEWEN: Yes. And I guess, also, if we're
25 talking about field studies with natural exposure, then there

1 are statistical power issues that are usually a major problem
2 there. And so, they need to be large in order to have much
3 chance of telling us things and that -- there are major issues
4 of cost and logistics.

5 CHAIRMAN MORRISON: Okay. Anymore comments on -- I
6 think, then, what we'll see here in a couple of slides -- is
7 that it for where we got yesterday other than general comments?
8 Dave.

9 DR. WHITE: Dave White, CVM. I think I'd like to
10 also mention somewhere in here, something that Dale brought up
11 about validation, standardization and reproducibility of these
12 tests, if it's an in vivo or in vitro. I mean, is this only
13 going to be done in this one lab or can I reproduce it in my
14 lab, and if we can't --

15 CHAIRMAN MORRISON: The need for standardization?

16 DR. WHITE: Yes; I would go with that.

17 CHAIRMAN MORRISON: Is that across all three studies,
18 Dave, or --

19 DR. WHITE: Yes.

20 CHAIRMAN MORRISON: So it's a general comment?

21 CO-CHAIRPERSON SINDELAR: A limitation?

22 DR. WHITE: I'd like to -- well, it's a limitation is
23 what I'm saying. It's the lack of standardization.

24 CHAIRMAN MORRISON: Difficulty of -- okay.

25 DR. WHITE: That's what I meant.

1 CHAIRMAN MORRISON: Okay. Okay. Good thinking.

2 DR. FEDORKA-CRAY: I think that you don't want to get
3 caught in saying that these have to be standardized for --

4 DR. WHITE: No; I wasn't getting that --

5 DR. FEDORKA-CRAY: Right; yeah, that the
6 reproducibility is probably going to be horrendous. If you go
7 to a field and you try to reproduce a field study, then what
8 you're saying is, is that -- for instance, when we go in and we
9 look at salmonella over time, and on a slide in particular that
10 I showed yesterday, it's rare that you're going to find the
11 same bacteria there all the time.

12 And each of the bacteria have different properties
13 with respect to resistance acquisition, acquisition of
14 resistance attributes, and so, if the demand is there for
15 reproducibility over time in field studies, that's going to be
16 very, very difficult to achieve for some of the zoonotics in
17 particular.

18 CHAIRMAN MORRISON: Impossible.

19 DR. FEDORKA-CRAY: It would be impossible.

20 CHAIRMAN MORRISON: Yeah.

21 DR. FEDORKA-CRAY: Exactly. And I think that's what
22 it comes down to. And even doing controlled, challenge type
23 studies, one of the things that you would have to ask yourself
24 in the field is, is how can you mimic all of the variables, you
25 know, even in -- when you do lab type studies and you're

1 talking about reproducing that, it becomes very difficult to
2 include multiple bacteria.

3 You can really only do that on a singular issue. You
4 know, you can't -- you don't have a very good idea what the
5 interaction is when you begin to add multiple bacteria to it.
6 So then, how do you, in essence then, design a study where all
7 of that can be evaluated because that's what's really happening
8 in the real world.

9 And the problem with the real world is, you can't
10 reproduce it all the time. So you have general ideas but when
11 you actually implement some things, then it doesn't -- it just
12 doesn't hold up. And one of the -- and so, I'll leave it at
13 that.

14 CHAIRMAN MORRISON: So the need for reproducible,
15 repeatable studies needs to be balanced against the breadth of
16 possible study factors out there and if you have a study that's
17 always repeatable, then you're not going to get very wide in
18 terms of your study factors?

19 DR. FEDORKA-CRAY: You're going to be limited in the
20 number of -- I don't want to say points because you're putting
21 the bacteria in, but the number of design factors that are
22 going to be able to be included in any one study is going to be
23 limited.

24 CHAIRMAN MORRISON: Yeah.

25 DR. FEDORKA-CRAY: And this is both in vitro -- I

1 mean, in the lab and in the field, too.

2 CHAIRMAN MORRISON: Did you get that?

3 MR. ANDRES: Yeah, I think I've got all that down.

4 CHAIRMAN MORRISON: Okay.

5 MR. ANDRES: That's what I have. I mean, Paula, you
6 give a suggestion how you want to capture that as a limitation
7 of the concepts that we heard Tuesday?

8 DR. FEDORKA-CRAY: I think --

9 MR. ANDRES: Or do you want it put under general --

10 DR. FEDORKA-CRAY: Well, yeah. I think that you
11 could put something -- no, I think it should go here, but I
12 think that you're going to have -- you would have to say
13 something like design -- you know, there will be something
14 about limitations in design. Yeah, I don't know that it's lack
15 of study and I'm just looking at that now. Lack of study
16 validation as opposed to something along the reproducibility
17 questions. Because each study is validated in itself, but you
18 don't -- you know, it's --

19 DR. BROWN: Scott Brown, Pharmacia & Upjohn. The
20 semantics I think we're trying to get at are important here, in
21 one respect that, what is reproducibility? Can you get the
22 same results, time after time after time after time with the
23 same study?

24 The second one, which I think a lot of used the word
25 validation for, is, do the results of this study infer

1 correctly what will happen in the field? The inference space
2 for these studies is a tremendous issue and I think that's the
3 part that some of us who were talking about validation were
4 concerned about, is the real inference space, from a
5 statistical perspective of these studies.

6 So one is reproducibility. Can you do the study?
7 Can you transport it to another lab? Can they get the same
8 result? And then the other one is the -- what can you infer
9 from these studies and is that -- has that been validated?

10 CHAIRMAN MORRISON: Do we mean by that, Scott, the
11 limited predictability?

12 DR. BROWN: That's a big part of it, yeah, I think
13 so.

14 CHAIRMAN MORRISON: I think we have that limited
15 predictability. Maybe what this point was trying to get at is
16 the need for reproducible lab protocols or the lack of --

17 DR. McEWEN: How about, to follow along with what
18 Paula was saying -- Scott McEwen again. How about as the level
19 of complexity of the experiments and studies increase, the
20 ability to reproduce them and validate them decreases?

21 CHAIRMAN MORRISON: Thank you. Wonderful.

22 (Pause.)

23 CHAIRMAN MORRISON: As soon as Chuck -- so I think
24 that finishes, I believe, our limitations that we listed. Is
25 that right?

1 MR. ANDRES: Yes.

2 CHAIRMAN MORRISON: Okay. The next question that
3 we're going to address is modeling. As we think about in
4 vitro, mathematical or perhaps in vivo, if you were going to do
5 a pig experiment in the pre-approval session, what factors
6 would you consider when modeling disease resistance or
7 antibiotic resistance?

8 And let's leave the pathogen load part out for now.
9 So what factors in your study design, as you listen to all of
10 those -- we're on question three now.

11 (Pause.)

12 CHAIRMAN MORRISON: I think, actually, what we've
13 done is, a lot of those limitations we were listing off as
14 advantages and disadvantages of different kinds of studies,
15 roles of data.

16 On that question two, what role could the various
17 types of data play in evaluating microbial effects? Are there
18 any additional comments?

19 (Pause.)

20 CHAIRMAN MORRISON: I think what's happened, Chuck,
21 is that in yesterday's discussion, we got to that question and,
22 if I remember correctly, what we've done is in some of our
23 points under limitations, those are actually referring to
24 different kinds of studies and the roles of those data.

25 (Pause.)

1 CHAIRMAN MORRISON: Aleta is confirming for me that
2 she feels we've answered a lot of two.

3 CO-CHAIRPERSON SINDELAR: It's just when we were
4 looking at the objectives of the pre-approval studies and we
5 were making comments, many of them, the purposes of the study
6 and the utility in like post-marketing surveillance, so I don't
7 want to inhibit any further discussion on number two.

8 I mean, if there are any other comments that you
9 would like to say that the role of the microbial effects would
10 play, please come forward and make that. We are really under
11 time constraints and we want to move forward on trying to
12 provide an answer to all five questions and any other issues.
13 But, if there are any additional comments on the roles, please
14 step forward and make them.

15 (Pause.)

16 CO-CHAIRPERSON SINDELAR: Okay. So let's move onto
17 question number three.

18 CHAIRMAN MORRISON: Okay. All right. So, question
19 three, there's really two types -- two subquestions. One is
20 regarding modeling resistance development and the other is
21 pathogen load changes. And so, what I would suggest is that we
22 first talk about what factors should be considered when
23 modeling resistance development.

24 This is sort of -- you know, you heard Paula and
25 different speakers yesterday say, here are all these issues

1 that influence the study outcome. And what I hear this
2 question telling us is, well, how would you rank these if you
3 want, and if you're going to go and model resistance
4 development, what are the really important factors that you
5 would incorporate into your study design?

6 DR. BROWN: Scott Brown, Pharmacia & Upjohn. I'm
7 struggling a little with knowing exactly what this question is
8 trying to head toward but let me take a stab at it and see if
9 I'm in the right direction.

10 If I understand risk assessments, and I had a lot of
11 experiences with mathematical modeling and pharmacokinetics,
12 one of the things that those two things together do is identify
13 a lot of assumptions and they also identify some of the
14 uncertainty with those assumptions and you can actually model
15 what tweaking some of those uncertainty areas will do to the
16 predicted outcomes.

17 To me, one of the things that could be done with both
18 of those, and I think it's nice to have both of them together
19 because they approach from completely different methods,
20 mathematically, and if you get the same kinds of results, then
21 you sort of have a lot greater comfort that you're in the right
22 direction.

23 I think what those two things could do, those two
24 tools could do, is to actually identify those factors that are
25 important in resistance development in swine and perhaps

1 pathogen load changes.

2 They would then be more vigilantly identified and
3 vigilantly monitored in the post-approval process. I would
4 strongly urge us not to say that those will be the things that
5 will impact on resistance development, but I think it's
6 important for us to say that those two tools might give us a
7 direction in which to look, ultimately, in the way that we
8 modify usage patterns and the way that we modify -- the way
9 that the antibiotic or the way that the particular usage is
10 being done in the field. So, I don't know if that's the right
11 direction that the question was intended, but that's --

12 CHAIRMAN MORRISON: And the two tools, one was
13 mathematical modeling and?

14 DR. BROWN: The other was risk assessment.

15 CHAIRMAN MORRISON: Risk assessment.

16 DR. BROWN: The compartmental modeling is the one I'm
17 thinking about that Dr. Lipsitch was talking about. They
18 really approach things very differently, both mathematically,
19 but with very different mathematical assumptions as part of the
20 Framework.

21 DR. McEWEN: Scott McEwen. I agree entirely with
22 what the other Scott just said, and I'd say that goes for all
23 the types of mathematical modeling, the pharmacokinetics,
24 pharmacodynamic, the risk assessment and the population
25 dynamics type modeling of Mark Lipsitch's.

1 But I would add to what he said in the sense that
2 these -- where possible these pre-approval studies and so on
3 should assemble data that could be used to fortify these types
4 of modeling to fit the parameters, too, and help us understand
5 the structure of these models.

6 So in a sense, the data gathering that is part of
7 this, these pre-approval studies, where possible, should be
8 designed with a view to helping us do the modeling.

9 CHAIRMAN MORRISON: The other -- we probably
10 shouldn't limit ourselves just to these mathematical analytical
11 models because another model that was presented I think was the
12 pig gut model, in vitro pig, sort of in vivo pig gut model.

13 DR. FEDORKA-CRAY: Paula Cray. I think, when I look
14 at this question, and it says what factors should be considered
15 when modeling resistance development and pathogen load, I guess
16 what comes to mind is, is that the complexity of design is
17 going to limit the applicability in answering how resistance
18 will develop in multiple -- in field environments, in the real
19 world, which is ultimately where you're taking it.

20 CHAIRMAN MORRISON: The complexity of design is going
21 to --

22 DR. FEDORKA-CRAY: Is going to limit.

23 CHAIRMAN MORRISON: -- limit it. Limit the --

24 DR. FEDORKA-CRAY: It's going to limit the, you know,
25 the applicability for taking the information and translating it

1 to the real world. I think that should just be recognized,
2 that all of those factors I talked about yesterday and really
3 -- and in talking about in developing animal models to look at
4 everything, and we just said -- we just went --

5 I mean, a lot of this I think we've talked about in
6 some of the other sections, that I've seen, that's already down
7 on paper. And you know what we're really addressing here is
8 the complexity going to be a limitation.

9 CHAIRMAN MORRISON: You're an expert and you've done
10 an enormous amount of work in this, if you were to say, what
11 are the top five factors that you think will have the most
12 effect on resistance development, what might those be? Out of
13 that complexity of nature out there and things that you'd love
14 to be able to understand, if there was five factors that you
15 thought, these are really important?

16 DR. FEDORKA-CRAY: In ten seconds or less?

17 CHAIRMAN MORRISON: Yeah.

18 DR. FEDORKA-CRAY: I would really hesitate -- I mean,
19 you know, I would hesitate to put down any factors. I mean, I
20 think the complexity issue is a factor itself, and I think that
21 if you -- you know, when you start looking, if you want to say
22 something very specific that you really can't pick five because
23 -- or you can't pick two or you can't -- because what ends up
24 happening is, is that they're all intertwined, you know, as
25 you're going down.

1 I mean, in just designing an animal experiment and
2 looking at age and -- I mean, this should be influenced by --
3 to me, if you have an indication for a particular drug, I mean,
4 we all -- I mean, I would always go back to, you have a drug
5 and you have a label indication.

6 The label indication is for a particular animal at a
7 particular age for a particular disease. Right? I mean,
8 that's the whole premise of this -- drug, animal, disease, and
9 it's going to be given for a certain period of time.

10 And so, how does that influence, then, what you're
11 going to essentially put into the herd or the pen or the
12 environment and predict what's going to happen next. And I
13 think that the complexity of that premise limits, you know, the
14 predictability.

15 CHAIRMAN MORRISON: Yeah. But let's say -- you know,
16 we saw a model yesterday; we saw population size -- you know,
17 the size of the herd or the, sort of the degree of
18 intermingling within a herd is going to influence it.

19 DR. FEDORKA-CRAY: Well, concurrent disease.

20 CHAIRMAN MORRISON: Age.

21 DR. FEDORKA-CRAY: Age, concurrent disease.

22 VOICE: Target pathogen.

23 DR. FEDORKA-CRAY: Target pathogen, stress.

24 VOICE: Disease background of the herd.

25 DR. FEDORKA-CRAY: Disease background of the herd.

1 VOICE: All 300 questions.

2 DR. FEDORKA-CRAY: All 300 -- yeah. I mean, I think
3 there was a list of twenty points that I put up -- genetics of
4 the herd, you know. And if you look at the farm design itself,
5 access to other animals.

6 CHAIRMAN MORRISON: Waste management system.

7 DR. FEDORKA-CRAY: Waste management. Management in
8 general.

9 DR. BROWN: --- mention drugs, Paula.

10 DR. FEDORKA-CRAY: Drug.

11 (Laughter.)

12 CHAIRMAN MORRISON: The drug.

13 DR. FEDORKA-CRAY: I did mention drug earlier. That
14 was acknowledged. I mean, I think that sometimes, like when I
15 see a question like this that's so broad, I mean, to me,
16 there's somewhat of a disconnect between -- here you're talking
17 about drug, bug, animal, a particular indication.

18 And now you want to throw in everything that happens
19 from, you know, time of farrowing through to the slaughter
20 plant and the predictability becomes really limited in that
21 scenario.

22 MR. ANDRES: Chuck Andres. I think maybe to pull the
23 scope in on the question a little bit, and I'll try to use
24 another analogy that maybe fits -- if you look at effectiveness
25 studies, okay? We certainly don't require that you test them

1 under all potential conditions of use prior to approval. It's
2 essentially a grab sample, if you will, of the environments
3 that this product could be used in. And I think the similar
4 type logic here is that, yeah, we could probably sit and go
5 through and list 300 factors that should be considered, and at
6 some point in time, when CVM sits down with a drug sponsor,
7 we're going to go through and say, okay, what's really doable?
8 What's really important when we start talking about these
9 factors? And that's where, from a guidance standpoint CVM's
10 trying to get your input as to --

11 DR. FEDORKA-CRAY: Okay. But see, but then the
12 frustration -- I'll just cut in right here then.

13 MR. ANDRES: Okay.

14 DR. FEDORKA-CRAY: Is that you're saying that this is
15 a scenario that you're going to operate under, and I would come
16 back to you and I would say that it would be totally dependent
17 upon the application that was being put forward.

18 MR. ANDRES: And I'd say, okay, fine.

19 DR. FEDORKA-CRAY: And so, I think that's where it
20 has to be recognized, the complexity of the design. I think
21 that these -- to go through some of these questions, they're
22 broad in itself, and what you're asking are for very specific
23 suggestions for scenarios that may change every time you walk
24 through that door.

25 And I think that, you know, that the presentations

1 yesterday certainly gave you that grab bag to pick from, so in
2 answering these types of questions, that the focus would be
3 more on the recognition that these -- that some of these types
4 of issues that we're approaching or that you're looking for
5 answers for, there may not be an answer that could be
6 applicable either across the board or an answer that can be had
7 at all.

8 But one of the things that I would, you know, caution
9 is, is just -- is trying to have an answer for everything when
10 there can't be an answer sometimes.

11 MR. ANDRES: But one of the exercises, I think, that
12 the breakout groups were trying to get -- are there -- what you
13 heard on Tuesday, I guess -- was it Tuesday? Is there specie
14 difference? We're talking -- this is the monogastric. We can
15 call it swine because if it was poultry, you would be over
16 there.

17 Are there factors that we should consider when you're
18 talking about swine studies? Swine drugs for use in swine that
19 we should consider, that should be considered when we talk
20 about modeling resistance development? Or is it --

21 DR. FEDORKA-CRAY: I think that those --

22 MR. ANDRES: -- universally, you know, the laundry
23 list of 300 things and it applies whether you're talking the
24 ruminant down at the other end, the avian or here or are there
25 differences?

1 DR. FEDORKA-CRAY: Okay. But maybe -- I mean, I'm
2 just -- I'm capturing that and saying that the complexity of
3 design mandates that the situations be evaluated on an
4 individual basis, and that when you look down through that
5 laundry list that that laundry list is going to -- you will --
6 that you'll have to pick and choose as you're going down
7 through for particular applications.

8 The very obvious ones are the ones that were just
9 listed. I mean, the management, the stress, the age of the
10 animal, the genetics, the management, proximity to other
11 animals, lagoon, waste management features, herd health.

12 CHAIRMAN MORRISON: I think just by listing them
13 we're answering this question, so -- because for all we know,
14 the people who are -- and it wouldn't surprise me at all -- the
15 people who are looking at this and evaluating this may not have
16 been on many farms. And so, I think it has value in just
17 listing these, and the fact that it's very complex. Scott.

18 DR. McEWEN: Scott McEwen. I've been trying to think
19 of something specific to swine and I can't think of anything;
20 maybe somebody else can, that all those things seem to apply to
21 all the food animal species.

22 And the second point is, I'm not sure we captured the
23 elements of Scott Brown's comments about the modeling. And
24 down below, mathematical modeling, and I would put in brackets
25 there, Pk, Pd, population dynamics, risk assessment.

1 MR. ANDRES: Say it again.

2 DR. McEWEN: Population dynamics, risk assessment.

3 DR. BROWN: The point that I was trying to make
4 earlier was that this mathematical modeling can identify
5 factors that we'd have to be on alert for, post-approval.
6 Under the bullet point just above that, the mathematical
7 modeling can identify factors that may substantially affect
8 resistance development, post-approval.

9 And I think, then, Scott McEwen's comment was that
10 the pre-approval studies, he would like to see them generate
11 data that would help feed into those mathematical models.

12 MR. SCHUSTER: Yeah, I'm finding this question
13 confusing as well and I think we're talking about two things
14 and it might be helpful to break them up. One would be animal
15 study type of models, how would you design a study in pigs?
16 Certain factors would apply to that.

17 Other would be more of a theoretical prediction and
18 that would be maybe a mathematical model or a risk assessment
19 type model or something. Maybe if we break out the factors in
20 both ways, it'll clarify that.

21 My own input is, if we're trying to predict a more
22 theoretically, key factors are class of drug. We know some are
23 more readily induced resistance than others. Another factor is
24 spectrum of activity, if it has activity against zoonotics or
25 not, or against commensals or not.

1 And a third factor would be gut exposure of the drug,
2 given its whatever route of administration. An injectable may
3 or may not give heavy exposure to the gut.

4 CHAIRMAN MORRISON: So those would be three key
5 elements that you would want to understand to build your
6 mathematical or risk assessment model?

7 MR. SCHUSTER: I think, theoretically, those three
8 factors could give you a sense of, is this a high, low or
9 medium level of concern of drug? If the drug didn't expose the
10 gut flora significantly, you might argue that there's no need
11 to do --

12 CHAIRMAN MORRISON: And those three factors, I'm
13 going to guess -- if we had another type of model being the pig
14 gut model that we heard about yesterday or the in vitro models,
15 not mathematical models, those three factors would influence
16 those, too, wouldn't they? Those three factors are pivotal to
17 any kind of model --

18 MR. SCHUSTER: Yes, but they'll come out. If you run
19 the study, they'll be built in as a matter of course. You
20 wouldn't have to worry about that in the design of the study.
21 You're going to know your route of administration and your dose
22 and whatever that should be is going to influence and you'll
23 get a readout.

24 But from that standpoint, I think key factors are
25 what species of organism are you looking at or are you going to

1 challenge it with, what specific strain, because we know
2 there's species and strain differences. I mean, dramatic
3 differences.

4 CHAIRMAN MORRISON: These are now pig model factors?

5 MR. SCHUSTER: These would be animal model factors.

6 CHAIRMAN MORRISON: Okay.

7 MR. SCHUSTER: Clearly, interactions or exposure to
8 an outside influences. If it's an isolated system or if it's
9 free to interact with all of the things, insects, birds,
10 residues from a previous study. I mean leftover manure or
11 contaminants, human interactions. So I would call that outside
12 interactions are clearly going to be key.

13 If you're a completely isolated system, you're
14 essentially doing something like an in vitro study where this
15 strain does or doesn't mutate to develop resistance with this
16 exposure, whereas if it's a more open system, say on a
17 commercial farm, you could be dealing with hundreds of
18 different strains and any one of them might be selected for or
19 not in the given study.

20 That's my short list of key factors and I might have
21 others if I give it more thought and I'm sure other people
22 might add some things, too. But, I think the complete list is
23 nothing short of 300 factors that we heard the experts say, and
24 I'm not qualified to say which of those are the most important.

25 CHAIRMAN MORRISON: So we've got our -- to put it

1 into three big categories, you've got your farm/environment
2 factors, a bizillion of them.

3 MR. SCHUSTER: Right.

4 CHAIRMAN MORRISON: You've got your drug factors,
5 which were the class of drug, the spectrum and the gut
6 exposure.

7 MR. SCHUSTER: Right.

8 CHAIRMAN MORRISON: And then you've got your strain
9 or species of organism factors.

10 MR. SCHUSTER: Yes.

11 CHAIRMAN MORRISON: The species of organism, the
12 strain of the organism and outside influences.

13 MR. SCHUSTER: And it's my view that certainly the
14 drug factors, and maybe if you're only interested in certain
15 zoonotics because of spectrum of activity or something, you
16 might have some sense of whether that needs to be investigated
17 with a study put in practice or just theoretically.

18 It's my view, if your drug doesn't expose the enteric
19 microflora to a significant extent, it's very unlikely to
20 select for resistance among the enteric zoonotics and it's very
21 unlikely to affect pathogen load.

22 Scott wants to open a can of worms that I'd rather
23 not go in. He's suggesting an environmental influence of the
24 drug, which I would consider that in an environmental safety
25 stuff and if we build in resistance there.

1 What we're focusing on in this conference is the
2 resistance selection and the target animal and that's what my
3 comments are limited to. I chose to limit it that way.

4 CHAIRMAN MORRISON: Good time for a coffee break, and
5 we'll try and catch up here.

6 (Brief recess.)

7 CHAIRMAN MORRISON: We've been talking about factors
8 that we would like to incorporate or we would like to consider
9 as we try to model resistance development and we had some
10 general comments with regards to this topic, that the factors
11 that affect the modeling may change from product to product,
12 that the complexity of the design, that these designs are going
13 to be incredibly complex, especially when you go to the field
14 and may limit the application, and that these mathematical
15 modeling can identify factors that may substantially affect
16 post-approval monitoring. Okay, Chuck; was there one more?

17 MR. ANDRES: Nope.

18 CHAIRMAN MORRISON: No? Okay. Then we said, well,
19 there's really three categories, or three if you lump these
20 factors into three categories, there's three categories. One
21 was the drug factors; two was the pathogen factors; and three
22 was the environment field factors.

23 Within drug, we said there's the class of drug, the
24 spectrum activity and the degree of gut exposure. Within the
25 pathogen, there was the species and strain. And then, with

1 environment, we just started listing them off and recognizing
2 we'll never get to all of them -- herd size, disease status,
3 genetics, waste management, herd management, feed source,
4 stress, the age profile, etcetera. Scott.

5 DR. McEWEN: Scott McEwen. I guess, technically, if
6 might be an advantage to take out some of the host factors and
7 make a host category because we have an agent category, an
8 environment category.

9 CHAIRMAN MORRISON: Oh yeah, that would be good.

10 DR. McEWEN: So there's like age and genetics and
11 that sort of thing.

12 CHAIRMAN MORRISON: True epidemiologist. That would
13 be great. So there's a fourth category of factors. There's
14 drug. There's the bacteria. There's the host and there's the
15 environment, and we'll pull out a few of those environment ones
16 and stick them into host like genetics, age, stress.

17 MR. ANDRES: So here you want to put --

18 CHAIRMAN MORRISON: So there's one more --
19 environmental field factors, another big bullet, host.

20 MR. ANDRES: I've got this duplicated so what I'm
21 going to do is what do we want to call --

22 CHAIRMAN MORRISON: Oh, okay.

23 MR. ANDRES: The fourth --

24 CHAIRMAN MORRISON: Host.

25 MR. ANDRES: Host; okay.

1 CHAIRMAN MORRISON: Delete herd size, delete disease
2 status, delete waste management, leave genetics, and make
3 stress and age, two. Stress and age. And I'm sure there are
4 others. Are there other big ones that occur to you as you
5 think about it as host?

6 VOICE: Immune status.

7 CHAIRMAN MORRISON: Immune status. Is that
8 stress/immune status? That's what really stress is, I think.
9 Or no? We can put two; I don't care. Stress, immune status.
10 Pardon?

11 DR. MUDD: Concurrent --

12 CHAIRMAN MORRISON: Concurrent infection? Health
13 status?

14 MR. ANDRES: Would you want that on both
15 environmental -- we've had --

16 CHAIRMAN MORRISON: Yeah, it really is both. One is
17 the health status of our individual pig and --

18 MR. ANDRES: Okay.

19 CHAIRMAN MORRISON: You can argue --- Paula?

20 DR. FEDORKA-CRAY: I think there's another -- if
21 you're going to talk about the target pathogen, a strain,
22 again, going back to the impact on human health, it's not the
23 target pathogen that's going to influence human health; it's
24 the zoonotic commensals and you have a species that strain
25 complexities -- your species is spelled wrong, too. It needs

1 and S. But you know, you have those factors, too, that you
2 have to consider.

3 CHAIRMAN MORRISON: And so, is there -- is the big
4 bullet where we have target pathogen is their agent and then
5 two subs, the target and --

6 DR. FEDORKA-CRAY: Right.

7 CHAIRMAN MORRISON: -- other organisms?

8 DR. FEDORKA-CRAY: Right.

9 CHAIRMAN MORRISON: Okay. Its agent as your big one,
10 and then you've got two subs of that, the target pathogen and
11 the other one is the human that you mentioned. Yes.

12 MR. ANDRES: I was just assuming we're talking about
13 zoonotics.

14 DR. FEDORKA-CRAY: Yes. And I think if we don't put
15 it up there, that's not the assumption. The other thing is
16 that I think that what factors should be considered when
17 modeling resistance development that I think that there is --
18 there are huge gaps in information that are available and I
19 think that should be acknowledged.

20 CHAIRMAN MORRISON: Up front in one the general
21 comments?

22 DR. FEDORKA-CRAY: Up front, that there are huge gaps
23 available -- I mean gaps and information.

24 MR. ANDRES: Okay.

25 CHAIRMAN MORRISON: Other comments, thoughts on this

1 issue of factors that we would consider as important in any
2 modeling attempts to study disease -- or antibiotic resistance?

3 DR. FEDORKA-CRAY: And I would make one other comment
4 -- it would just be a comment that I think that, especially
5 something like this, would beg for a small group interaction to
6 ferret out study design.

7 (Pause.)

8 CHAIRMAN MORRISON: After a little bit of espionage,
9 I find out we're in the running for first place. We're doing
10 very well.

11 VOICE: No surprise, is it?

12 CHAIRMAN MORRISON: What? Yeah. Among the other
13 groups, we're apparently doing well. It's very important that
14 we win.

15 (Laughter.)

16 CHAIRMAN MORRISON: Okay. Paula had a point in here
17 -- huge gaps in information. Huge gaps in information require
18 specific studies to address them.

19 DR. FEDORKA-CRAY: I don't think -- I think part of
20 the problem with a lot of the models that are developed is that
21 you have this information gap and it leads to assumptions and
22 so, a lack of information may complicate --

23 CHAIRMAN MORRISON: Interpretation?

24 DR. FEDORKA-CRAY: -- interpretation -- study design
25 and interpretation.

1 CHAIRMAN MORRISON: Dave.

2 DR. WHITE: Yeah; I was going to wait for the next
3 slide.

4 CHAIRMAN MORRISON: Okay.

5 DR. WHITE: Or the -- I guess it's this slide but
6 there's another -- the last bullet I wanted to mention. It's
7 not up there yet, so -- when we were talking about what Paula
8 mentioned before, the specific pathogen, we've also been, you
9 know -- also been talking about potentially looking at
10 commensal and I wouldn't call a commensal a pathogen.

11 CHAIRMAN MORRISON: We are going to -- in the next
12 question we are going to be talking a lot about what pathogens
13 should we focus on, how should the appropriate pathogen be
14 selected and should surrogate organisms be used?

15 DR. WHITE: Well, I was thinking, here, instead of
16 target pathogen, if you want to say target bacterium. I mean,
17 I'm not --

18 CHAIRMAN MORRISON: Okay.

19 DR. WHITE: You know -- because I'm not sure what
20 we're --

21 DR. FEDORKA-CRAY: That's much better.

22 DR. WHITE: I'm not sure what we're going to pick
23 yet.

24 CHAIRMAN MORRISON: Target bacterium.

25 MR. ANDRES: Target zoonotic ---

1 DR. WHITE: Yeah. Parentheses, zoonotic or commensal
2 or something like that.

3 CHAIRMAN MORRISON: Okay. Target bacteria, and then
4 in brackets, zoonotic and commensal. No, up on the top line in
5 brackets.

6 CO-CHAIRPERSON SINDELAR: No.

7 DR. FEDORKA-CRAY: No; just leave it like that and
8 then go down to zoonotics/ --

9 CHAIRMAN MORRISON: Oh, okay. Or couldn't it just be
10 target, zoonotic/commensal?

11 DR. FEDORKA-CRAY: Uh-huh. It could be -- you just
12 have one.

13 MR. ANDRES: Commensal --

14 CHAIRMAN MORRISON: Target -- we're going to change
15 it.

16 MR. ANDRES: Oh, we're going to change it?

17 CHAIRMAN MORRISON: Target, zoonotic, commensal and
18 species, and then just take --

19 MR. ANDRES: Okay.

20 (Pause.)

21 MR. ANDRES: Is that better?

22 CHAIRMAN MORRISON: Okay. So we've got drug factors,
23 agent factors, host factors, environment factors and we have
24 some general comments. One of the things that we talked about
25 earlier, the other part of this question is, what are the

1 factors that you would consider when you were designing your
2 pathogen load studies?

3 And this group said -- there were mixed feelings on
4 the pathogen load studies and one of the comments was, we
5 really need or perhaps should urge FDA/CVM to have a separate
6 conference/session/something on pathogen load.

7 So talking with Aleta earlier, she said, you know, if
8 there are pressing comments with regard to factors that one or
9 more of you think we should incorporate into study design, we
10 can put them here or we can just say, we think pathogen load is
11 big enough and important enough a topic that it should be
12 addressed as a separate workshop; whichever you prefer.

13 MR. SCHUSTER: Dale Schuster, Schering-Plough. I
14 think we've talked enough. Let's not schedule another workshop
15 and put down our thoughts now and see how it comes out.

16 CHAIRMAN MORRISON: Okay. And so, if pathogen load
17 was to be incorporated into pre-approval studies, what factors
18 would you think are important?

19 DR. BYWATER: Robin Bywater, Pfizer. I think we said
20 earlier that the pathogen load studies don't make a lot of
21 sense for short term therapeutic product, at least not to my
22 mind. I think we're talking much more about long term feed
23 medication or growth --

24 CHAIRMAN MORRISON: So you would speak for not
25 putting them in -- not spending time now?

1 DR. BYWATER: Well, no, it's just sort of making the
2 point that the pathogen load studies, perhaps, are not
3 particularly relevant for short term therapeutic type drugs.

4 DR. McEWEN: Scott McEwen. I think a lot of the
5 previous factors would relate to pathogen load as well.
6 There's the drug factors, and Robin's point is -- relates to
7 that and then there's the host agent/environment issues as
8 well. So, my sense is, all of the above relate to pathogen
9 load.

10 CHAIRMAN MORRISON: Okay.

11 MR. SCHUSTER: Dale Schuster again. Maybe under
12 drug factors you can add duration of treatment or dose regime.
13 I would also add a withdrawal period. I think that's
14 especially relevant for pathogen load. If your withdrawal
15 period is extended, I think it becomes a nonissue very easily.

16 CHAIRMAN MORRISON: So two to add under the drug.

17 MR. ANDRES: Oh, you want --

18 CHAIRMAN MORRISON: No, you can just add them under
19 the drug.

20 MR. ANDRES: Add them?

21 CHAIRMAN MORRISON: Yeah.

22 MR. ANDRES: Okay.

23 CHAIRMAN MORRISON: The duration.

24 MR. SCHUSTER: It would be treatment duration.

25 CHAIRMAN MORRISON: And the withdrawal period.

1 MR. SCHUSTER: The title of that section, resistance
2 modeling, we can -- just put key factors, whatever.

3 CHAIRMAN MORRISON: In modeling --

4 MR. SCHUSTER: Because resistance and pathogen load
5 modeling are just key factors. Just above drug factors, the
6 title, drug factors. I mean, that's a given.

7 MR. ANDRES: What I could do is -- what I thought,
8 we're going to separate them because there's so much comment on
9 keeping the two, resistance and pathogen load separate, but if
10 you want --

11 CHAIRMAN MORRISON: There was a comment that they
12 overflow so much --

13 MR. ANDRES: -- just go back to the title and the
14 question and I'll remove --

15 CHAIRMAN MORRISON: Is there a feeling that we should
16 -- is there some feeling in here that we should not separate
17 them? I'm sorry -- that we should separate them? We've heard
18 the feeling that we should just lump them. Okay. Let's just
19 lump them.

20 MR. ANDRES: Great.

21 CHAIRMAN MORRISON: Dave, unless you were going to
22 speak towards --

23 MR. SCHUSTER: I had something else I wanted to add.

24 CHAIRMAN MORRISON: Okay.

25 MR. SCHUSTER: And that was, my view on this, like

1 the drug factors, the exposure to the gut, the withdrawal
2 period, are all going to be known and may preclude the need to
3 do and in vivo study.

4 And all of these factors, that would be known up
5 front, combined with what we know about the categorization and
6 the exposure might preclude the need to do in vivo studies, and
7 only a restricted few high concerning situations would actually
8 warrant doing an in vivo study if any did, if we could even
9 come up with a in vivo study that --

10 CHAIRMAN MORRISON: If I understand your comment, and
11 if I understand this question, is if you were try to and
12 design, whether it be a mathematical or a pig gut model or
13 whatever kind of experiment, what would you incorporate into
14 your design? You'd look at these factors and decide which ones
15 of them are important?

16 MR. SCHUSTER: Yeah, and the first cutoff might be a
17 risk assessment, saying does this particular drug use scenario
18 present enough concern that we need to look into it further?

19 CHAIRMAN MORRISON: Okay.

20 DR. WHITE: Can we go back to the last slide, Chuck,
21 real quick? Here under agent factors, I wasn't sure if we
22 wanted to think about, since we're modeling resistance,
23 resistance mechanisms. You know, known resistance mechanisms
24 or transfer. Do we want to add this under a description under
25 an agent factor or is this something we're already thinking

1 about, under an agent -- you know what I mean?

2 CHAIRMAN MORRISON: So, it's propensity to --

3 DR. WHITE: Well, I would say known resistance
4 mechanisms or --

5 CHAIRMAN MORRISON: Known resistance --

6 DR. WHITE: Maybe just mechanism resistance, period,
7 and then --

8 CHAIRMAN MORRISON: Of this organism? Or of this --

9 DR. WHITE: Of your --

10 CHAIRMAN MORRISON: Of this agent?

11 DR. WHITE: Of the target or the commensals or
12 zoonotic. You know, is there literature out there, there have
13 been studies done that have described the mechanism and -- I
14 don't want to get too much into the genetics of it, but you
15 know, mechanisms and transfer.

16 CHAIRMAN MORRISON: Okay.

17 DR. WHITE: These are things we were trying to think
18 about earlier.

19 CHAIRMAN MORRISON: Anything else on factors that you
20 think would be important to consider if you were to try and
21 model disease resistance? I'm sorry -- antimicrobial
22 resistance or pathogen load studies? If not, we go to the next
23 question, what pathogens should be the focus of pre-approval
24 studies?

25 And then the second question, how should the

1 appropriate pathogen be selected? And the third question is,
2 should surrogate organisms be used? So what pathogens should
3 be the focus of pre-approval studies? And I'm guessing this
4 question refers to other than your target.

5 MR. ANDRES: (Inaudible comment.)

6 CHAIRMAN MORRISON: Well the target -- and so I would
7 say, the target, and, what other pathogens? It begs the
8 question -- well, assuming -- do you support the concept that
9 there are other pathogens that should be considered?

10 DR. McEWEN: Scott McEwen. I mean, to me, it's the
11 zoonotic enterics mainly, so, campylobacters, salmonella,
12 possibly the list would then go on from there in some cases,
13 maybe --

14 MR. ANDRES: Zoonotic enterics.

15 DR. McEWEN: Some E.coli. I mean, the question for me
16 is where you draw the line between calling something a zoonotic
17 and then a commensal or a surrogate or indicator. Like in some
18 instances, E.coli could be both a commensal and a zoonotic.
19 For pigs, it's -- to my mind, it's not a zoonotic.

20 It would be a commensal or indicator. Enterococci,
21 you could argue that in some instances it could be a zoonotic.
22 Probably others would argue that it's not; it's really a
23 commensal. So, I think the main ones I would put down would be
24 campy and salmonella and then see what other people about other
25 zoonotics.

1 DR. FEDORKA-CRAY: I think we're going to run into a
2 problem here, though, where if you say zoonotic enterics and
3 you say campy, you mean campy coli or you mean campy jejuni?
4 Because campy coli is, you know, more prevalent in swine than
5 in other species.

6 Campy coli is not supposed to be implicated in human
7 health, so do you want to look at that? Do you have to look,
8 then, for herds that have an effect on -- you know, or have
9 jejuni in that, how do you screen those? The same thing comes
10 down with salmonella, which strain do you use?

11 Which strain are you looking for? Which phage type
12 are you looking for in all of this? And I think that this was
13 -- this is sort of like the crux of the whole initial workup in
14 there is that what are you actually going to pick? And
15 then, there's some discussion about the -- when you look at the
16 commensal bacteria, or you look at not necessarily commensal
17 but you look at the enteric, or the surrogates. Are surrogates
18 predictive of a human health hazard and how do you assess that?
19

20 And where do you come up with that information ahead
21 of time? So, I would -- I mean, I would have another comment
22 in there that qualifies that the selection of a pathogen and/or
23 commensal may be problematic in that there are multiple strain
24 and species within each category or genre.

25 CHAIRMAN MORRISON: Given that, would you go beyond

1 the target? Are you speaking for -- maybe we ought to just
2 stop at the target.

3 DR. FEDORKA-CRAY: Well, I mean, I think this goes
4 back to whole question, again, of what are you trying to -- you
5 know, what pathogens should be the focus of a pre-approval
6 study and I'm not sure there should be a pathogen that we need
7 to look at for a pre-approval study because all you're looking
8 at is the bug that you're putting forth for the application.

9 Now if you're looking at a risk to human health, then
10 what do you target? And yes, you would target the zoonotics
11 and yes, you might target some of the commensals. Then I would
12 say that the difficulty occurs that within, say swine, you
13 know, is campy coli relevant?

14 And are you going to get enough information to know
15 that campy jejuni is a -- I mean, do you need to do all of the
16 studies for campy jejuni, knowing that the likelihood of campy
17 jejuni showing up in swine is very, very small. I mean, you
18 know, what percent is relevant? And then again, with
19 salmonella, is what strain are you selecting, you know?

20 CHAIRMAN MORRISON: So are you speaking -- would you
21 say -- you would suggest, do you have the opinion that we
22 should do the target and only the target?

23 DR. FEDORKA-CRAY: I would suggest that the target
24 should be listed and that the statement, the selection of
25 pathogen or commensal may be problematic, given the different

1 strains, serotypes, phage types, etcetera. Yeah, that may --

2 CHAIRMAN MORRISON: Preclude going beyond the target?

3 DR. FEDORKA-CRAY: That may preclude -- right. That
4 may preclude going beyond the target in that relevant
5 information may not be possible.

6 CHAIRMAN MORRISON: So there's no evidence that we
7 know of that indicates that there's an indicator zoonotic
8 pathogen?

9 DR. FEDORKA-CRAY: I wouldn't want to -- you know,
10 the most important pathogen for swine is colarsuis and
11 colarsuis is very -- has a very, very low prevalence in the
12 human population. You say titanarium, which is, you know, in
13 both, but you know, we have more and more evidence that phage
14 types are playing a big role.

15 Do you take titanarium? Do you take titanarium
16 copenhagen? And we know that all titanariums aren't equal
17 either. I mean, which one are you going to select? And I just
18 think that we need to, up front, say that this is -- the
19 selection is excruciatingly difficult.

20 DR. McEWEN: Scott McEwen. I like the excruciating
21 part.

22 (Laughter.)

23 DR. McEWEN: I think we need -- I think we could
24 acknowledge something that was mentioned in the risk assessment
25 document, is that there's a -- I think CVM has given

1 consideration to a sentinel organism, maybe one that's either -
2 - one or two that either are -- most of the
3 food-borne diseases attributed to it and/or resistance, there's
4 a propensity for developing resistance and the --

5 Acknowledging the inability to look at all
6 combinations of organisms and serotypes and that sort of thing,
7 that I think there were thoughts given to using this sentinel
8 as kind of one that in a sense errs on the side of safety, but
9 you can imagine industry's concern that that might set
10 inappropriately high standard.

11 So I think there is that possibility as a way of
12 getting around this issue that Paula has raised of -- an
13 enormous number of different strains and so on; how do you --
14 where do you start?

15 MR. WHITE: If I go back to what I reiterated before,
16 maybe instead of what pathogen in the title, it should just be
17 what bacteria should be the focus of pre-approval studies?

18 And also, in terms of -- the question like Paula was
19 mentioning, with coli as relevant to human health, I think
20 that's a good question because it may not play a role in terms
21 of disease but what if it's a reservoir of resistance genes for
22 jejuni? I mean, these are things I just think we need to take
23 into account. That's all.

24 CHAIRMAN MORRISON: What was the second point, Dave?
25 I'm sorry. About the reservoir?

1 DR. WHITE: Yeah. I mean, when we're talking about
2 other organisms, that may not be the particular pathogen ---
3 some of these animal analogs or the animal equivalent. Are
4 they potential reservoirs of resistance genes that could be
5 transferred to the pathogen we're interested in in the
6 pre-approval study or whatever we're going to do post-approval
7 monitoring on? So I don't know if that confuses it or --

8 CHAIRMAN MORRISON: Is that reservoir a point that
9 refers back to our agent in the last section or is it here, or
10 both?

11 MR. ANDRES: It's here.

12 CHAIRMAN MORRISON: Here.

13 DR. WHITE: Yeah, I guess.

14 CHAIRMAN MORRISON: Here. Okay.

15 DR. WHITE: I guess I'd like to hear from the group,
16 I guess, on this one. I just -- I didn't mean to open a can of
17 worms. I just wanted to -- there's other things to think about
18 relevance in terms of just overt disease, that we also could
19 think about possibly as this reservoir of resistance now.

20 DR. BROWN: Scott Brown, Pharmacia & Upjohn. I guess
21 one of the things I'm struggling with is knowing which
22 pre-approval studies we're talking about that these pathogens
23 ought to be looked at because, in one instance, we're looking
24 at sort of a rate and extent of the development of resistance.

25 And if that's the case, it's, at least in my feeble

1 mind, possible to identify a -- sort of a strain type that
2 would be a -- almost like a QC organism that you know what it's
3 likely mutation frequency is and that sort of thing and could
4 have some positive/negative controls that you understand that
5 organism well enough that you can test your particular compound
6 and see whether your compound is a rapid producer of resistance
7 or not.

8 It might or might not have any relevance in terms
9 of whether it produces disease. On the other side of it, the
10 pre-approval studies, if they're designed to establish baseline
11 resistance in sort of the field -- I use the word field very
12 reservedly -- in the sort of all the population, I think that's
13 a different issue and then you do have to kind of wonder, which
14 one's are you looking for?

15 But I wonder if it's not possible to look at sort of
16 an ATCC well-defined strain of something or other that would be
17 genetically similar and really characterize it well and then
18 use that one as the organism that you would look at in terms of
19 the mutation frequency onset and rate of resistance and that
20 sort of thing.

21 DR. FEDORKA-CRAY: This is Paula Cray again. I see
22 where you're coming from, Scott, but I just would -- can you
23 find that strain? I mean, that would be -- and is an ATCC
24 strain -- I mean, one of the problems with ATCC strains that we
25 have is that they tend to be attenuated.

1 They tend to be -- you know, they don't mimic
2 anything that is going to translate in the real world
3 situation. I mean, they're often used as QC because of their
4 stability type issues, not because they're reflective of
5 anything that might be happening in a real world type
6 situation.

7 So I would just -- I mean, I would just question
8 who's going to do all the studies to find that strain and, you
9 know, what strain do you select and -- I mean, you know, all
10 of those types of issues.

11 DR. BROWN: That's why you get paid the big bucks,
12 Paula.

13 (Laughter.)

14 DR. FEDORKA-CRAY: Oh yeah, big bucks.

15 CHAIRMAN MORRISON: So did I get that right, Dave? I
16 substituted bacteria and then we're going to have a target and
17 then selection of others depends upon which pre-approval study
18 is being considered?

19 DR. WHITE: Yes.

20 CHAIRMAN MORRISON: Okay. And then, if you're going
21 to select one, the selection of other pathogens may be
22 problematic, a given? So there's an if statement -- if you're
23 going to do it, okay, now it's difficult and then you get into
24 a slippery slope, down which you have to figure out, okay,
25 where are we going to stop? Okay.

1 DR. McEWEN: Scott McEwen. Well, I wonder about
2 including a bullet or line, just saying we discussed the
3 strengths and limitations of a sentinel in quotation marks or
4 prototype or model organism or organisms.

5 DR. BYWATER: Robin Bywater, Pfizer. I mean, I think
6 the archetypical sense in all of this is E.coli. It's the one
7 you can find everywhere, leaving entirely aside whether it's
8 anything to do with source of resistance or whether it's a
9 pathogen in a pig, it's still a very convenient sentinel
10 organism and if you're really wanting just to see what was
11 happening in terms of resistance selection and the enteric
12 flora, why go any further? And it's there in every animal for
13 you to look at.

14 DR. WHITE: Dave White. One thing, that would be, of
15 course -- this may fit into the choice of an organism might
16 depend, of course, on the spectrum of the activity of the
17 antimicrobial. I mean, if it's gram positive, we're not going
18 to look at campylobacter, salmonella or we shouldn't. I mean,
19 if it's a macroli, we shouldn't look at salmonella; we probably
20 should look at campy. And if it's gram positive, maybe we need
21 to pick it -- look at enterococci or staphylococci.

22 CHAIRMAN MORRISON: Sorry. The next question being,
23 how -- no, no. Yeah, that's the one we're on now, what
24 pathogens. I'm sorry. Were you referring to go onto --

25 MR. SCHUSTER: His answer fits in the next question.

1 CHAIRMAN MORRISON: Number five?

2 MR. SCHUSTER: No. How should appropriate pathogens

3 ---

4 CHAIRMAN MORRISON: Okay.

5 MR. SCHUSTER: Is there a ---

6 CHAIRMAN MORRISON: Sure. With my dual purpose, I
7 missed your statement.

8 DR. WHITE: Me?

9 CHAIRMAN MORRISON: Yeah.

10 DR. WHITE: Is, we should just take into
11 consideration what the spectrum of activity of the
12 antimicrobial to be assayed or analyzed or tested or what.
13 Gram positive versus gram negative would influence what
14 organisms we would choose. I think that was a problem with the
15 old 558.15 studies, obviously.

16 MR. ANDRES: Consider the spectrum of activity of the
17 antimicrobial. What would be a better way to describe that?

18 CHAIRMAN MORRISON: Other comments on really any
19 question within here? What pathogen should be considered?
20 What we're talking about now is how should the pathogen. If
21 you were going to select something else, how would it be
22 considered? And maybe we could put in the four (c) now, should
23 surrogate organisms be considered? Again, we sort of bounced
24 around this issue. Are there specific comments on that?

25 DR. McEWEN: Scott McEwen. It's not entirely clear

1 to me what's meant by surrogate. I guess --

2 CHAIRMAN MORRISON: I guess non-pathogens.

3 DR. McEWEN: Well, one interpretation of surrogate
4 could mean what we were talking about before about having a
5 model strain or one that's well understood and that we're going
6 to make the assumption that that's representative of the
7 spectrum of pathogens. That could be seen to be a surrogate
8 organism. Another interpretation could be, a surrogate could
9 be as an indicator organism.

10 The presence of this resistance in say E.coli could
11 be used as an indicator of what would likely happen in
12 pathogens which is hard --- as a commensal as a possible donor
13 of determinants, that sort of thing. So, I think we need some
14 clarification about that or else give alternative explanations
15 there.

16 CHAIRMAN MORRISON: Scott, you mentioned --

17 DR. McEWEN: The sentinel --

18 CHAIRMAN MORRISON: Yeah, the sentinel indicator
19 bacteria, that we just move that.

20 DR. McEWEN: Well, I guess all I'm saying is, is
21 there one sort of definition/interpretation of surrogate
22 organism or do we have different possible interpretations and
23 I'm just saying that, in my mind, it's not a specific term for
24 one.

25 It could be either -- a surrogate organism could be

1 what's called a sentinel organism, I think, and in a campy risk
2 assessment, that's one that either is most of the food-borne
3 disease or a large proportion of food-borne disease is
4 attributable to it, or it's one that has a propensity for
5 resistance development and so we'll use that as our -- I hate
6 to use the word -- the phrase worst case scenario, but one that
7 errs on the public health side of things.

8 That's a possible use of a surrogate. Another one is
9 as Scott Brown suggested, ATCC type strain, well characterized,
10 would allow us to do reproducible studies and ones that could
11 be interpreted across laboratories. That would be a possible
12 surrogate.

13 And a third type of surrogate could be, as I think
14 Robin was suggesting, that is an organism like E.coli which is
15 -- its presence is widespread. It's easily cultured. Its
16 resistance in that organism could be interpreted to be an
17 indicator of what might happen in enteropathogens or it could
18 be interpreted to be just an alternative species.

19 I'm not quite sure. So I'd see those three
20 different, at this point, three different possible types of
21 surrogate organisms.

22 MR. SCHUSTER: Let's not worry about the definition.
23 Which would you want to use?

24 DR. McEWEN: So the question is, which would we want
25 to use and I guess, you know, not speaking as an advocate,

1 necessarily, of public health here, but one I think defensible
2 use of a surrogate would be to, as is identified in the campy
3 risk assessment, that first definition I gave, an organism that
4 is -- to which a lot of food-borne disease is attributed and/or
5 -- and it could be the same organism.

6 There's a propensity for resistance development. And
7 I invite other people to say that that's not appropriate or we
8 should have -- we prefer another type of surrogate.

9 CHAIRMAN MORRISON: Chuck has asked the question, do
10 we -- this question says, should organisms be -- should
11 surrogate organisms be used? Yes or no? And --

12 MR. SCHUSTER: That's -- I mean, if we don't know
13 just how to define it, that's why I thought we --

14 MR. ANDRES: Okay. If yes, then these three
15 considerations? I mean, I'm just trying to -- how best to
16 present.

17 MR. SCHUSTER: Yeah; Dale Schuster. I thought, since
18 we're not sure what's the definition of surrogate we would put
19 in, what would be appropriate alternatives to a real world
20 pathogen or, you know -- including a laboratory strain of a
21 real world pathogen.

22 CHAIRMAN MORRISON: And so, that --

23 MR. SCHUSTER: This would -- where we would define
24 what would be an acceptable surrogate and --

25 CHAIRMAN MORRISON: Okay.

1 MR. SCHUSTER: -- if that's not a surrogate in your
2 mind, then we don't support it; we support this. And I agree
3 with Dr. McEwen; I think that appropriate strain and species of
4 a zoonotic pathogen with a known understanding of its ability
5 to resistance development, I guess I would lean for one not
6 that's not particularly high or low but middle of the road, but
7 definitely a zoonotic species, not something that doesn't cause
8 disease.

9 MR. ANDRES: Right.

10 DR. BROWN: Scott Brown, Pharmacia & Upjohn. I would
11 agree with both what Dale and what Scott McEwen have said. I
12 think the other -- the only caveat I would have is that if --
13 unless we have something that we have identified and is
14 something that is -- I use the word standardized again, then
15 five years from now it'll be a different strain and then the
16 criteria for what is appropriate or inappropriate changes, and
17 then we're left with a continuing changing set of criteria.

18 So I would propose that yes, it be a zoonotic
19 organism; that yes, there's a known capacity for it to develop
20 resistance and we can argue whether it's high, medium or low,
21 but at least it's defined and then it's a strain that becomes
22 very well characterized and is the same strain used, regardless
23 of whether it's compound X or compound Y, or maybe there's a
24 particular categorization of compounds that use that particular
25 strain.

1 DR. BYWATER: Robin Bywater, Pfizer. Well I can see
2 the attraction in a very general way. I have a problem
3 envisaging the actual experiment that would be done. I'm
4 talking about challenging a group of animals with this
5 organism, getting it established and then exposing it to the
6 drug? Possible but not easy, as Paula described yesterday.

7 I actually quite like the idea of a sentinel
8 organism, sentinel species, because it's there and you don't
9 have to put it there; and therefore, I would be very wary about
10 setting up a requirement of the kind of studies that would be
11 practically very difficult to achieve, but I may be missing the
12 point.

13 DR. MCEWEN: Scott McEwen. I think it's fair to
14 present as certainly a reasonable alternative. I mean,
15 somebody's going to have to decide which way to go and there's
16 -- both of those are rational and I'm sure there are three or
17 four others that are rational.

18 CHAIRMAN MORRISON: Has Chuck captured these three
19 correctly? That if a surrogate is one of these three, then you
20 can see logic behind it. That if it was an indicator with
21 propensity for resistance or if it could be ATCC, well
22 characterized, well understood bacterium or you could argue it
23 could be -- it should be an E.coli, ubiquitous present
24 resident. Those are the three that we've said, if that's what
25 a surrogate is, we can see the logic behind it.

1 DR. McEWEN: Scott McEwen. One further thing --
2 E.coli, I guess I'd ask the question if that would be
3 appropriate for say gram positive drugs? So, E.coli or
4 enterococci, but the general idea of a ubiquitous commensal
5 organism.

6 CHAIRMAN MORRISON: Equally gram negative or -- just
7 so you remember. Other comments on this whole topic of should
8 pathogens be the focus -- what pathogens should be the focus of
9 pre-approval? How should the appropriate pathogens be selected
10 and should we have surrogate organisms? That's what we're
11 talking about.

12 DR. McEWEN: Scott McEwen. Did we answer the middle
13 question?

14 CHAIRMAN MORRISON: We had one suggestion from Dave
15 White, I believe, one slide up.

16 DR. McEWEN: I guess I would suggesting adding
17 importance to human health.

18 CHAIRMAN MORRISON: Is there logic within this
19 question of the prevalence or how common this pathogen is out
20 there in the industry? Does that impact whether you would
21 include it or not?

22 DR. McEWEN: Well, to me, it's implicit in the
23 importance part of it. Important implies that it's virulence
24 and --

25 CHAIRMAN MORRISON: Oh, okay.

1 DR. McEWEN: -- the spectrum of disease in people but
2 also it's frequency and degree of transfer and amount of
3 exposure that people are faced with.

4 MR. SCHUSTER: I would just add that importance and
5 importance being relative to swine being a source. I mean, if
6 it was important but it comes from chickens --

7 CHAIRMAN MORRISON: Yeah. Under importance,
8 there's --

9 MR. SCHUSTER: So just add that caveat as source from
10 swine or something like that.

11 MR. ANDRES: Okay.

12 CHAIRMAN MORRISON: Yeah.

13 MR. ANDRES: Swine or monogastrics?

14 CHAIRMAN MORRISON: Swine.

15 DR. WHITE: Dave White. I guess to expand on what
16 Dale was saying, are you trying to get like association with a
17 particular animal species of the pathogen? So maybe pathogen
18 association with historically or -- I mean, one question
19 luckily we don't have to deal with is aquaculture. I don't
20 know what you would pick for surrogate or pathogens if you
21 looked at aquaculture products.

22 MR. ANDRES: That's in another --

23 DR. WHITE: I know. I'm saying, luckily it's not us,
24 but --

25 (Laughter.)

1 VOICE: That's in another room.

2 (Laughter.)

3 DR. WHITE: I'll sit down.

4 CHAIRMAN MORRISON: Chuck, let's go back to the
5 beginning of four.

6 MR. ANDRES: Okay. Number four.

7 CHAIRMAN MORRISON: So to review question four, then,
8 what pathogens should be the focus of the pre-approval studies?
9 We said -- we changed pathogen to bacteria and we said, well
10 obviously the target organism. And then, the selection of
11 other bacteria really depends upon which pre-approval study was
12 being considered.

13 One might consider a sentinel or indicator bacteria
14 and if you were to select other pathogens, we talked about this
15 almost being a slippery slope about how far are you going to
16 go? How are you going to select -- a very difficult, complex
17 question. Let's go to the next one, Chuck.

18 How should the appropriate bacteria be selected, the
19 spectrum of activity and the importance to human health. And
20 the last one, should surrogate organisms be used? We were
21 unclear on the definition of surrogate.

22 We would support it or there was support in the
23 room, in general, if it included either an indicator with a
24 propensity for resistance, either a well-characterized ATCC
25 bacteria, or something that was ubiquitous and well understood.

1 Other comments on question four?

2 The last question is, alternative approaches,
3 concepts that we have not talked about. Now, we've thrown a
4 few of these ideas, probably into general, so we may have had
5 some things come up but just in sort of a brainstorming way.
6 Are there things that we've missed that have occurred to you?
7 Alternative approaches, concepts that have not been considered,
8 presumably for pre-approval.

9 DR. VAUGHN: Michael Vaughn with Bayer Animal Health.
10 What we've gone through the last couple of days really
11 highlights the complexity of all this pre-approval discussions
12 and what ought to be done, and I guess the next challenge for
13 CVM is to sort through all this and to see if pre-approval
14 studies are going to be pivotable, are going to be information
15 gathering and what role they might play in assessing the
16 approval of new antimicrobials and the impact they have on
17 resistance in zoonotic and human health and so forth.

18 So it's going to be a tremendous challenge for them.
19 And they may conclude that it isn't -- the pre-approval
20 studies may not contribute anymore into their decision making
21 process as to whether they will approve an antimicrobial and
22 they may focus more on the post-approval process.

23 And as the body of information is gathered post-
24 approval, then they could maybe better assess the impact it's
25 going to have. And we also can't forget the risk assessment

1 model that we discussed in December, and as that risk
2 assessment model matures, based on the comments that were
3 gathered last week, or I guess today -- today is the final day
4 for the comment.

5 And as that risk assessment model matures, then it
6 may be a real positive tool to be in this whole process, too,
7 and we may focus less on these pre-approval studies.

8 CHAIRMAN MORRISON: So Michael, your comment is that
9 over the last day or so, you've wondered about that FDA/CVM
10 might consider all of these discussions in light of the role of
11 pre-approval as opposed to post-approval and risk assessment?

12 DR. VAUGHN: Correct. And you know, the final
13 decision may hinge on the complexity of all these and we may
14 never be able to come to a conclusion that pre-approval studies
15 ought to be used in the approval process, the final approval
16 process of an antimicrobial, you know.

17 We may ask for further information that can be
18 plugged into a risk assessment model or like was brought out
19 yesterday, some of the information that we're going to gather
20 in these pre-approval studies may help direct us just to where
21 we need to go on our post-approval monitoring process.

22 You asked for any additional things, I think we need
23 to not forget that we have a risk assessment model that is in
24 the developmental phase and that we are probably going to
25 reconsider the role that these post-approval monitoring

1 programs are going to have in the decision making process, and
2 ultimately, that may be what we need to focus on.

3 CHAIRMAN MORRISON: So maybe what you're saying is it
4 might be a shame to cast our pre-approval process in stone
5 before we work through these other parts of it.

6 DR. WHITE: And I think that as CVM assesses what
7 went on in all these groups, and it was necessary, you know,
8 and I think -- and I really appreciate Paula being here today.
9 She really brought home the complexity of all this.

10 You know, there aren't really simple answers maybe to
11 all these questions that we want to answer as to -- and as CVM
12 assesses it -- and I'm glad they have that job and not me, this
13 is a very complex issue.

14 And as they assess that, we may focus more on the
15 risk assessment in the post-approval as a process to monitor
16 and evaluate resistance in human health issues.

17 CHAIRMAN MORRISON: Okay.

18 MR. FONDRIEST: Steven Fondriest, Union of Concerned
19 Scientists. While I haven't been working in this issue very
20 long, it has been going -- from what I've seen, it's been going
21 on for -- this process, now, over a year?

22 An alternative that would work, it is simple, would
23 be simply -- is to categorize antibiotics, would be to ban the
24 ones that are being used in human medicines that are very
25 important for human medicine that are also being used

1 subtherapeutically in livestock.

2 It's an issue that has not really been discussed at
3 all at this meeting over the past three days and I think you
4 should consider it. Post-approval studies, pre-approval
5 studies, risk assessment, this all has been going on for quite
6 a long time and it's likely to continue for a long time.

7 Dealing with resistance development is going to --
8 resistance development is going to occur in antibiotics that
9 are used in livestock and it's going to adversely affect
10 humans.

11 We could ban certain antibiotics now, ban the use of
12 them as subtherapeutics and we could solve -- begin to solve
13 this problem and I would urge CVM to do that now, not wait
14 another year to categorize antibiotics and how they're being
15 used, the risk to humans, and ones where risk is unacceptable,
16 ban them. It's simple in practice.

17 CHAIRMAN MORRISON: So you would expedite this whole
18 process by simply banning subtherapeutic use of drugs that are
19 used in humans?

20 MR. FONDRIEST: Where there's significant risk to
21 human health, we could ban them now and we could solve that
22 problem.

23 MR. ANDRES: Define significant --

24 CHAIRMAN MORRISON: Chuck is asking if you would
25 define the significant risk to humans.

1 MR. FONDRIEST: I think the risk assessment addresses
2 it as significant, or the Framework discusses significant
3 impact to humans and I would think that would be something that
4 the Food and Drug Administration could define and then --

5 CHAIRMAN MORRISON: Okay.

6 MR. FONDRIEST: -- we could criticize that later.

7 MR. ANDRES: Okay.

8 MR. FONDRIEST: But, define it first for us and we'll
9 give you an answer on what we think, if it's a realistic
10 definition of significant.

11 CHAIRMAN MORRISON: Okay.

12 MR. SCHUSTER: You have subtherapeutic --

13 MR. FONDRIEST: Initially, yeah, I am addressing --
14 yeah, that's subtherapeutic use, for now.

15 DR. BYWATER: Robin Bywater, Pfizer. I mean, this
16 suggestion does beg a whole lot of questions. We're here to
17 decide on a process for regulatory approval of new compounds,
18 not what to do about the old ones, specifically.

19 And also, the question about what is the significance
20 of the risk to human health is certainly one which is a matter
21 still of debate rather than established fact.

22 DR. McEWEN: Scott McEwen. I would agree that this
23 statement should probably go on the comment section. I mean, I
24 don't see -- I guess maybe we could ask Steven to defend
25 whether he thinks it's an alternative approach for pre-approval

1 or it's a comment. I guess the one thing that I would suggest
2 is --

3 CHAIRMAN MORRISON: If you can stop right there, just
4 for a second. Let's finish that thought because your point, I
5 think, is an important one, that the comment -- or this process
6 is about new, pre-approval process for new drugs.

7 MR. FONDRIEST: Yeah, you're right, but I would say
8 yes.

9 CHAIRMAN MORRISON: So we're looking at alternative
10 approaches for pre-approval of new drugs. That's what this is
11 about.

12 MR. FONDRIEST: Right. Well I think, first of all --
13 thanks for bringing that up, Robin. Yes, pre-approval, and
14 this is a comment dealing with the pre-approval approach and it
15 should be extended.

16 It should also deal with the drugs that are already
17 registered because we're basically -- the barn door is open,
18 the cow is out of the barn and we're not going to be able to
19 put him back in unless we do something now and that would
20 require addressing the antibiotics that are presently in use.

21 And I don't think this is just a comment; this is an
22 alternative. I mean, yes, it is a comment but this is an
23 alternative to dealing with the pre-approval program is we
24 could nip it in the bud now and just ban, outright, certain
25 antibiotics used in subtherapeutic applications.

1 CHAIRMAN MORRISON: If I can -- under this point, I
2 think what you're getting at is to now allow new
3 subtherapeutics that pose a significant risk. Now you may have
4 a general comment for existing that perhaps can go perhaps in
5 the general comment but if you want --

6 MR. FONDRIEST: Okay. That would --

7 CHAIRMAN MORRISON: Okay.

8 MR. ANDRES: Is what I have -- I've made one word
9 change up here to make it appropriate for this discussion as
10 far as pre-approval, categorize new antibiotics and their use
11 in humans and would be prohibit and not approve the
12 subtherapeutic use?

13 CHAIRMAN MORRISON: Yeah, not approved.

14 MR. FONDRIEST: Right, not approved.

15 MR. ANDRES: Because you're not banning it; you're
16 prohibiting it.

17 DR. McEWEN: Scott McEwen. I just have on that we
18 could consider as an alternative approach and it may be
19 implicit in some of the previous things but I kind of like the
20 idea of testing a bank of organisms, presumably
21 enteropathogens, zoonotics, that have been collected as part of
22 the NARMS and other surveillance systems, and screening them
23 for the genetic determinants of resistance to a drug under
24 application to establish the sort of baseline of resistance or
25 lack of it out there.

1 Now that may already be part of what's proposed
2 elsewhere, but I find that sort of an appealing -- it came out
3 yesterday, to some extent --- approach.

4 CHAIRMAN MORRISON: To test a bank of organisms for
5 resistance to the drug being applied for or --

6 DR. McEWEN: Right. Presumably, during the
7 development process, the genetic mechanisms of resistance would
8 be determined and we'd have a test developed for identifying
9 those determinants and that it shouldn't be too onerous to
10 screen a bank of organisms that we've collected as part of
11 the human and animal, food animal surveillance from NARMS
12 and establish a baseline that would then help with the
13 post-approval monitoring, foreseeing if there has been an
14 increase, and help to establish this temporal business that's
15 been so much at issue with fluoroquinolones. But it would --
16 you know, applies to all the drugs really.

17 MR. ANDRES: Is that accurate?

18 CHAIRMAN MORRISON: Well, and maybe the last part is
19 to establish a baseline --

20 MR. ANDRES: Okay.

21 CHAIRMAN MORRISON: -- for post-approval
22 surveillance.

23 MR. SCHUSTER: If I could add a comment to Scott's as
24 well as -- I know there are some companies that are -- think
25 about hiring people to kind of reverse resistance. I mean,

1 make it in the laboratory first before you observe it out in
2 the field so that you would have the mechanism identified first
3 and it's like engineer resistance or something. You know what
4 I mean? Actually, when I interviewed at Pfizer, that was going
5 to be what I was going to do --

6 (Laughter.)

7 DR. WHITE: It seemed like a good idea at the time.
8 Here's a new antimicrobial coming through the pipeline. Let's
9 see if I can make it resistant in the lab. Then we
10 characterized the mechanism and we know maybe that's what's
11 going to happen out in real life, so I don't -- I don't know
12 the -- I wasn't looking for -- what's that?

13 VOICE: (Inaudible comment.)

14 DR. WHITE: It depends upon -- well, no. If you have
15 a bank of isolates, maybe it will. So I mean -- I don't mean
16 one strain, an ATCC strain, you know what I mean?

17 CHAIRMAN MORRISON: So it was to cause or initiate or
18 simulate or to something resistance and then to the proposed
19 compound and then study the mechanism. Is that right, Dave?

20 DR. WHITE: Yes.

21 CHAIRMAN MORRISON: And study the mechanism by which
22 it -- to the proposed product and then study the mechanism.

23 MR. SCHUSTER: I wanted to make a comment here at the
24 end, not so much as an alternative approach, although we might
25 put it in there, but more to get the sense of what are the

1 important things that our group feels?

2 We have twenty-one slides. We present these, our key
3 factors are going to get lost in the details. In my own mind,
4 and I think I'm supported by at least a few of my colleagues --
5 the key point of this is that based on the discussions we've
6 had on Tuesday and yesterday and our own internal thoughts, is
7 that pre-approval studies are not in any way going to be able
8 to predict the rate or extent of resistance development.

9 I want that made very emphatic. There is no evidence
10 that we can do any pre-approval study that will accurately
11 predict the rate and extent of resistance development.
12 Therefore, public health cannot be based on using pre-approval
13 studies as a safeguard.

14 It doesn't really make sense for them to be pivotal
15 if they aren't telling us a whole lot. The appropriate
16 approach that I see, and you might call it an alternative
17 approach, is to use the surveillance, post-approval
18 surveillance, the NARMS program to protect public health.

19 Pre-approval studies should consist of the
20 information gathering type of studies that we outlined, the in
21 vitro studies, and only the extremely few studies that look
22 particularly concerning might be subjected to more detailed
23 investigation to provide some assurance that it's not going to
24 be a disaster after it's approved.

25 I think it's very important to get this message

1 across. Which pathogens we use and whether we use surrogates
2 and all such things as that, we're all going to come to a
3 consensus on that and not argue to significant extent.

4 But clearly, the --- of pre-approval studies is a
5 very contentious issue and I don't think they can be designed
6 in a way to truly protect public health alone.

7 MR. ANDRES: Is that emphatic enough?

8 MR. SCHUSTER: That looks very encouraging. Thank
9 you.

10 (Laughter.)

11 MR. ANDRES: Is that accurate, that first one?

12 MR. SCHUSTER: Tony Mudd is proposing that we make
13 that as a concluding remark. That's fine. My concern is that
14 the point is made very clearly. I would be inclined to do it
15 up front, to put the rest into context and to avoid the very
16 likely possibility that we don't get around to it because we
17 get hung up on the details that are presented to us.

18 DR. BYWATER: What about ---

19 CHAIRMAN MORRISON: Is there anybody in the group
20 that doesn't share that opinion?

21 DR. McEWEN: Scott McEwen. I agree, it's the
22 statement that the studies probably can't be used to accurately
23 predict the rate and extent. I wouldn't go so far as to say
24 that they're useless because I don't think we know that.

25 CHAIRMAN MORRISON: I didn't hear that.

1 DR. McEWEN: And that wasn't said; I know that. So I
2 wouldn't -- I mean, I wouldn't buy into the notion that because
3 of this we reject a notion of doing pre-approval studies, and
4 again, that wasn't said, but I wouldn't want that to appear,
5 from my perspective.

6 DR. WHITE: Dave White. Could I add a comment that
7 maybe you want to say pre-approval studies cannot, at this
8 time?

9 MR. ANDRES: That's fine.

10 DR. WAGNER: Dave Wagner, CVM. I'm just wondering if
11 you want to modify this a little bit to also include an
12 alternative, then, to pre-approval studies?

13 CHAIRMAN MORRISON: I heard the alternative which we
14 haven't got written yet. Was that -- or that these studies
15 could be used, as we've said -- as a few in vitro studies to
16 identify major warnings, etcetera, and to guide the -- what you
17 would regard as the important or more important portion of the
18 drug approval process being the surveillance post-approval
19 NARMS type surveillance project.

20 MR. SCHUSTER: Yes. Essentially the objective would
21 be to do the baseline information that will support that
22 because that is the public health safeguard.

23 CHAIRMAN MORRISON: Is it fair to say that these
24 studies could be used to identify major or somehow to identify
25 the major -- you want to screen out, if they haven't already

1 been screened, products that, holy smokes, there's a huge red
2 flag here, or -- and/or, more importantly, to develop the
3 necessary information for the post-approval surveillance. Is
4 there two parts to that? Is it --

5 MR. SCHUSTER: I'll defer on the first one. The
6 second one, I think, is absolutely --- but the main objective
7 is to support --

8 CHAIRMAN MORRISON: Develop the information
9 required/useful for post-approval surveillance.

10 DR. McEWEN: Scott McEwen. I'd like to capture that
11 first statement of yours, Bob. Probably in a sense that, you
12 know, CVM should seek to identify -- I'm looking for a word
13 other than red flag but I think that's maybe a good one to use.
14 Just red flags in brackets -- in quotation -- in inverted
15 commas, for drugs where there's -- I guess the sense is that
16 there's a propensity for resistance and a public health threat
17 that's of such magnitude that it --

18 CHAIRMAN MORRISON: That's the essence of that.

19 DR. McEWEN: I'm grappling for the words, obviously.

20 MR. SCHUSTER: I would prefer that the support for
21 pre-approval is made as a strong bullet. The red flag, I'm not
22 convinced yet from the data that we have, that we can even do
23 that and that would be like a possible objective if we can
24 envision the right scenario.

25 My concern is if we did mutation studies and

1 transmission studies, we can't ignore those that show --
2 mutations to resistance is extremely common and it can spread
3 across any pathogen imaginable. I mean, that would be the
4 case, but --

5 CHAIRMAN MORRISON: Yeah. Does that capture it? To
6 require/useful for post-approval surveillance and possibly
7 identify major red flags?

8 MR. SCHUSTER: Yes.

9 CHAIRMAN MORRISON: Okay.

10 MR. SCHUSTER: That looks good.

11 DR. SUNDBERG: Paul Sundberg. And I'm going to
12 suggest that that may be a step back from where we -- we're
13 stepping back to say, well, possible major red flags, then --
14 I thought we were at the point where it wasn't going to be
15 a pass/fail, that it was a vector, vectoring situation for
16 post-approval surveillance rather than a pass/fail.

17 CHAIRMAN MORRISON: You're worried that if we have a
18 red flag, then red flag is a matter of judgment, whose red flag
19 it is?

20 DR. SUNDBERG: Yeah. And it just seems that that's a
21 step back from what we've been trying to do.

22 DR. McEWEN: Scott McEwen again. I'm not sure that
23 it's implied that that's necessarily a pass/fail, and maybe
24 some more words are required but I would -- I mean, I could
25 envisage a process where some major concerns are identified and

1 then maybe there's an --- approach taken with the industry to
2 further substantiate those concerns.

3 But as a screening exercise, presumably what you'd
4 like to have is a mechanism that has high sensitivity, in
5 quantitative terms, not in human concerns -- in terms -- high
6 sensitivity for identifying possible major public health
7 threats.

8 And then that doesn't imply that that the screening
9 test is pass/fail, but then it's -- I would imagine that
10 there's a working with the industry to sort of reconcile those
11 concerns.

12 DR. BYWATER: Robin Bywater, Pfizer. I wonder
13 whether the red flag could be defined as having identified
14 a major red flag that could lead to the need for further
15 pre-approval studies to be carried out so that the red flag
16 wouldn't necessarily say you're out the door but it might well
17 say you've got some indications here that really need to be
18 further investigated before -- in the pre-approval process
19 before you go onto --

20 CHAIRMAN MORRISON: So just to add that it might
21 require further studies?

22 DR. BYWATER: Further studies in the pre-approval
23 process or further pre-approval studies.

24 CHAIRMAN MORRISON: Okay.

25 DR. BYWATER: I mean, I think that goes -- it shows

1 us there's a reaction to these initial results without
2 necessarily bringing back this pass/fail criterion that we
3 thought perhaps wasn't appropriate earlier on.

4 MR. ANDRES: Remove the word major?

5 DR. BYWATER: Yes.

6 CHAIRMAN MORRISON: Oh, okay. Removed the word major
7 and added that could lead to additional pre-approval studies.
8 Paul. We're wearing people down.

9 (Laughter.)

10 CHAIRMAN MORRISON: Other thoughts? So we've had
11 these major sort of overarching conclusions. I agree with you
12 wholeheartedly, we'll get lost in the minutiae and you want to
13 take away two or three points and the rest of it's all here.
14 Are there other major overarching points that people share or
15 alternatives, to go back to our question five?

16 MR. ANDRES: We've got four things. Do you want to
17 review what we have for five right now?

18 CHAIRMAN MORRISON: These are alternative
19 approaches/concepts that have not been considered, one; that in
20 light of everything we've done, we would like to make sure that
21 the role of these pre-approval studies is considered in light
22 of the post-approval and risk assessment. I think there was
23 two, not just post-approval, risk assessment, but if I remember
24 correctly, it was post-approval, surveillance and risk
25 assessment.

1 MR. ANDRES: Well, pre and post versus --

2 CHAIRMAN MORRISON: It's the role of the pre-approval
3 study process needs to be considered in light of the
4 post-approval process and risk assessment.

5 VOICE: The post-approval monitoring.

6 CHAIRMAN MORRISON: Monitoring.

7 VOICE: The risk assessment --

8 CHAIRMAN MORRISON: Studies.

9 MR. ANDRES: Studies. Post-approval, monitoring and
10 risk assessment.

11 CHAIRMAN MORRISON: Secondly, that something we
12 hadn't talked about was that a bank of organisms might be
13 tested for resistance to provide a baseline for post-approval
14 surveillance.

15 Thirdly, that this process could be expedited if new
16 antibiotics that were going to be used in humans were simply
17 prohibited for subtherapeutic use. Fourthly, if we could
18 engineer resistance in the lab to the proposed product and
19 study the mechanism, that might be revealing.

20 DR. WHITE: Actually I wanted to make a comment on
21 that -- if we could maybe add a caveat and say this may not be
22 possible for all antimicrobials?

23 MR. ANDRES: Okay.

24 DR. WHITE: Under that one.

25 CHAIRMAN MORRISON: If possible, engineer the

1 resistance?

2 MR. WHITE: If possible.

3 CHAIRMAN MORRISON: Other thoughts, alternative
4 approaches that we've not considered?

5 MR. SCHUSTER: Can we just go over the first three
6 slides?

7 MR. ANDRES: All right. That's the first slide.

8 CHAIRMAN MORRISON: You've got me worried. Oh, this
9 first slide. I see it. Okay.

10 MR. SCHUSTER: When this is presented, I'd make sure
11 the yes is what we were told by FDA and not what --

12 CHAIRMAN MORRISON: Oh, yeah. That's good. We were
13 told yes. Okay.

14 MR. SCHUSTER: And maybe the second point could be
15 our view ---

16 DR. McEWEN: Could we say some in the group? I'm not
17 sure that there's unanimity on that.

18 DR. SUNDBERG: I was going to say, speak to the same
19 thing, that perhaps, Bob, when you present this, we don't need
20 to put it in there, but our protocols may be a little bit
21 different than other groups, whereas we have included
22 statements from individuals.

23 We've included statements that we -- everybody's kind
24 of nodded their head at, but at some point, it's not a
25 consensus, to point out that we didn't reach consensus on all

1 these and then, so the some in the group type of thing.

2 CHAIRMAN MORRISON: Okay. You're thinking, Dale,
3 everybody will doze off after about this point?

4 (Laughter.)

5 MR. SCHUSTER: These aren't really what --

6 CHAIRMAN MORRISON: Biggies; yeah.

7 MR. SCHUSTER: -- the messages are and I want to be
8 sure that they're clear and that we review them and agree that
9 --- represents our consensus and our ---

10 CHAIRMAN MORRISON: Chuck, could you go to the
11 general slides? I'm wondering if some of those general slides
12 shouldn't be up front, perhaps right behind our immediate --
13 our biggie.

14 DR. McEWEN: Well, you know, I'm not so confident
15 that, Bob, you won't be able to emphatically present all of our
16 deliberations here. I think you will be able to, so -- I mean,
17 I agree that having a couple up front is good to underscore
18 them but I -- we don't have so much information that you will
19 be overwhelming folks, I don't think.

20 CHAIRMAN MORRISON: Okay.

21 MR. WHITE: There's actually an hour and a half
22 scheduled for that.

23 CHAIRMAN MORRISON: And I'm assuming you all are
24 going to be there to --

25 MR. SCHUSTER: That's twenty minutes a group.

1 MR. ANDRES: Yes. Well, you've got a minute a slide.

2 MR. SCHUSTER: I guess I'm not sure what the first
3 bullet there is. I thought that's what we're ---

4 MR. ANDRES: Who made that comment?

5 CHAIRMAN MORRISON: Was that Steven?

6 MR. ANDRES: Wanted to have specific workshops on --

7 DR. SUNDBERG: Actually what it was was an attempt to
8 get us off the --- on pathogen load and say if we can't reach
9 something, then let's have a workshop on it.

10 CO-CHAIRPERSON SINDELAR: On pathogen --

11 CHAIRMAN MORRISON: Oh, on pathogen load?

12 MR. SCHUSTER: That was pathogen load. And there was
13 the -- we should do it; we shouldn't do it; we can do it; we
14 can't do it. If we can't decide or we don't have the
15 information, then let's get the mechanism by which we can get
16 an informational system to make a decision.

17 CHAIRMAN MORRISON: Is there a feeling on whether
18 these general slides should be up front or at the back or do
19 you care? Don't care. Okay. I'm going to turn the floor back
20 to you.

21 DR. BYWATER: I think we should also --- above the
22 discretion of dropping some of these bits and pieces that don't
23 fit into the flow of your presentation. I don't think you
24 should necessarily feel you've got to give every little bit
25 that we've gone through.

1 CHAIRMAN MORRISON: I'll work -- I'm guessing Chuck
2 and I are going to sit -- and Aleta are going to sit and go
3 through this. Any changes that look, you know, important at
4 all, we won't make. If something just doesn't flow, we'll try
5 and make a few word changes, if you'll give us that --

6 MR. SCHUSTER: I would like to thank you. I've heard
7 other groups have not been as smooth. I thought that this was
8 a very good way of bringing things up and you've got --- I
9 thank you very much.

10 (Applause.)

11 CO-CHAIRPERSON SINDELAR: Thank you. We actually
12 have until 12:30. If there are any other comments, please make
13 them now. Otherwise, we will go to the task of summarizing
14 this for preparation of -- you know, at 2:00.

15 MR. ANDRES: At 2:00, yep.

16 CO-CHAIRPERSON SINDELAR: And we'll all be back in
17 the Regency Room at 2:00. Thank you.

18 (Meeting was recessed, to reconvene for group
19 presentations, Regency Room, 2:00 p.m.)
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